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PATENT TRADEMARK OFFICE

Attorney's Docket No.: GNVPN.031USA 09/807802
JC03 Rec'd PCT/PTO 17 APR 2001TRANSMITTAL LETTER TO THE U.S. ELECTED OFFICE
(EO/US) - ENTRY INTO NATIONAL STAGE UNDER 35 USC 371PCT/US99/25694
International Application No.2 November 1999
International Filing Date5 November 1998
Priority Date ClaimedADENO-ASSOCIATED VIRUS SEROTYPE I NUCLEIC ACID SEQUENCES,
VECTORS AND HOST CELLS CONTAINING SAME

Title of Invention

James M. Wilson and Weidong Xiao
Applicant(s) for EO/USBox PCT
Assistant Commissioner for Patents
Washington, DC 20231
Attn: EO/US

Sir:

Applicant herewith submits to the United States Elected Office
(EO/US) the following items under 35 USC 371:

- (1) This express request to immediately begin national examination procedures (35 USC 371(f)).
- (2) A copy of the cover sheet for the published International Application along with a copy of the specification as filed: 109 pages, including 5 pages of claims, 13 sheets of drawings, 59 pages of Sequence Listing, and a copy of the 4 pages International Search Report.
- (3) a copy of the 5 page Request form.
- (4) a first Preliminary Amendment for entry prior to calculation of the filing fees.
- (5) our check in the amount of \$1,420.00, covering the basic national fee as set forth in 37 CFR 1.492(a)(5) and based on the first Preliminary Amendment (16 total claims; 10 independent; and no multiple dependent).
- (6) A Second Preliminary Amendment.

Express Mail No.

ET03364824345

- (7) Our check in the amount of \$90.00, covering the extra claim fees after entry of the second Preliminary Amendment (25 total claims; 10 independent; and no multiple dependent).
- (8) Two (2) pages partially-executed Combined Declaration and Power of Attorney form by first inventor.
- (9) A 59 pages Sequence Listing (provided in specification).
- (10) A 3.5" computer-readable diskette.
- (11) A 1 page Statement under 37 CFR §1.821(f) and §1.825(a) and (b).

Copies of the following miscellaneous items are also enclosed:

- (12) Copy of the 3 page Demand for International Preliminary Examination.
- (13) Copy of the 10 page Written Opinion.
- (14) Copy of the 11 page International Preliminary Examination Report.

The Combined Declaration and Power of Attorney form of the second inventor will be filed by the appropriate deadline under 37 CFR §1.495(c)(2) with the surcharge under 37 CFR §1.492(e).

Please charge any additional fees which may be required to effect entry into the National Phase and credit any overpayment to Deposit Account No. 08-3040.

Please direct all communications concerning this application to the undersigned.

Respectfully submitted,
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GNVPN.031USA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of) Group Art Unit:
)
James M. Wilson et al) Examiner:
)
Appln. No. 09/807,802)
)
Filed: April 17, 2001)
)
For: ADENO-ASSOCIATED VIRUS) February 20, 2002
SEROTYPE I NUCLEIC ACID)
SEQUENCES, VECTORS AND HOST)
CELLS CONTAINING SAME)

Commissioner for Patents
Box Sequence
Washington, DC 20231

STATEMENT PURSUANT TO 37 CFR §1.825(a)&(b)

Sir:


A substitute Sequence Listing and a computer readable form of the substitute Sequence Listing are provided herewith. This Sequence Listing contains updated background information and is in PatentIn Version 3.1. No substantive changes have been made. The substitute Sequence Listing and computer readable copy contain no new matter.

This affirms that to the best of my knowledge and belief the content of the pages of the substitute Sequence Listing and this computer readable copy of said pages of the substitute Sequence Listing provided herewith are the same.

Respectfully submitted,

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GNVPN.031USA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of) Group Art Unit:
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James M. Wilson et al) Examiner:
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Appln. No.)
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Filed: Herewith)
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For: ADENO-ASSOCIATED VIRUS) April 17, 2001
SEROTYPE I NUCLEIC ACID)
SEQUENCES, VECTORS AND HOST)
CELLS CONTAINING SAME)

Assistant Commissioner for Patents
Washington, DC 20231

PRELIMINARY AMENDMENT

Sir:

Please amend the application as set forth below.

In the Claims

Cancel claims 7, 8, 12, 13, 15, 21 and 22 without prejudice.

REMARKS

After entry of this preliminary amendment, the pending claims are claims 1-6, 9-11, 14, 16-20, and 23. Claims 7, 8, 12, 13, 15, 21 and 22 are cancelled. No new matter is introduced by this preliminary amendment.

Express Mail No. ET03364824345

Applicants respectfully request that this preliminary amendment be entered prior to calculating the filing fees.

The Director of the U. S. Patent and Trademark Office is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees to Deposit Account No. 08-3040.

Respectfully submitted,

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000071202 09/807802

JC02 Rec'd PCT/PTO 17 APR 2001

GNVPN.031USA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of) Group Art Unit:
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James M. Wilson et al) Examiner:
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Appln. No.)
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For: ADENO-ASSOCIATED VIRUS) April 17, 2001
SEROTYPE I NUCLEIC ACID)
SEQUENCES, VECTORS AND HOST)
CELLS CONTAINING SAME)

Assistant Commissioner for Patents
Washington, DC 20231

SECOND PRELIMINARY AMENDMENT

Sir:

Please amend the application as follows.

In the Specification

Page 1, line 6, before "Field of the Invention", insert the following new paragraph:

-- Cross-Reference to Related Applications

This is a 371 of PCT/US99/25694, which claims the benefit of the priority of US Patent Application No. 60/107,114, filed November 5, 1998. --

Please enter the attached Abstract of the Disclosure on the attached page as new page 38.

Express Mail No ET033648243US

In the Claims

Add new claims 24-32 as follows.

24. The recombinant vector according to claim 3, wherein said vector further comprises AAV-1 capsid proteins having the sequence of SEQ ID NO: 13, 15 or 17 or functional fragments thereof.
25. The recombinant vector according to claim 3, wherein said vector further comprises adenovirus sequences.
26. The host cell transduced with a recombinant viral vector according to claim 3.
27. The host cell transduced with a nucleic acid molecule according to claim 1.
28. The host cell transduced with a nucleic acid molecule according to claim 2.
29. The host cell transduced with a nucleic acid molecule according to claim 10.
30. The host cell transduced with a nucleic acid molecule according to claim 11.
31. The pharmaceutical composition comprising a carrier and a virus comprising the vector according to claim 3.

32. The method for delivery of a transgene comprising the step of delivering to a host cell a recombinant virus comprising a recombinant vector according to claim 3.

REMARKS

Upon entry of this preliminary amendment, the claims pending are claims 1-6, 9-11, 14, 16-20, and 23-32. New claims 24-32 are supported throughout the specification and additionally by now cancelled original claims 7, 8, 12, 13, 15, and 22, respectively. New claims 24-32 have been added to incorporate the subject matter of canceled claims 7, 8, 12, 13, 15, and 22, as well as to correct dependencies. No new matter is introduced by this preliminary amendment. A clean copy of all of the pending claims is attached as Appendix A.

The attached Abstract of the Disclosure is supported throughout the specification.

Applicants respectfully request consideration of the amended pending claims.

The Director of the U. S. Patent and Trademark Office is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing, or during prosecution of this application to Deposit Account No. 08-3040.

Respectfully submitted,

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[illegible]

1. An isolated AAV-1 nucleic acid molecule comprising a sequence selected from the group consisting of:
 - (a) SEQ ID NO: 1;
 - (b) a DNA sequence complementary to SEQ ID NO: 1;
 - (c) cDNA complementary to (a) or (b); and
 - (d) RNA complementary to any of (a) to (c).
2. A nucleic acid molecule comprising an AAV-1 inverted terminal repeat (ITR) sequence selected from the group consisting of:
 - (a) nt 1 to 143 of SEQ ID NO: 1;
 - (b) nt 4576 to 4718 of SEQ ID NO: 1;
 - (c) a nucleic acid sequence complementary to (a) or (b); and
 - (d) a functional fragment of (a), (b), or (c).
3. A recombinant vector comprising a 5' AAV-1 inverted terminal repeat (ITR) and a selected transgene, wherein said ITR has the sequence selected from the group consisting of:
 - (a) nt 1 to 143 of SEQ ID NO: 1;
 - (b) a nucleic acid sequence complementary to (a); and
 - (c) a functional fragment of (a) or (b).
4. The recombinant vector according to claim 3, wherein said vector further comprises a 3' AAV-1 ITR.

5. A recombinant vector comprising a 3' AAV-1 inverted terminal repeat (ITR) and a selected transgene, wherein said ITR has the sequence selected from the group consisting of:

- (a) nt 4576 to 4718 of SEQ ID NO: 1;
- (b) a nucleic acid sequence complementary to (a); and
- (c) a functional fragment of (a) or (b).

6. The recombinant vector according to claim 5, wherein said vector further comprises a 5' AAV-1 ITR.

9. A recombinant vector comprising an AAV-1 P5 promoter having the sequence of nt 236 to 299 of SEQ ID NO: 1 or a functional fragment thereof.

10. A nucleic acid molecule encoding AAV-1 helper functions, said molecule comprising an AAV rep coding region and an AAV cap coding region, wherein said cap coding region comprises at least one member is selected from the group consisting of:

- (a) vp1, nt 2223 to 4431 of SEQ ID NO: 1;
- (b) vp2, nt 2634 to 4432 of SEQ ID NO: 1; and
- (c) vp3, nt 2829 to 4432 of SEQ ID NO: 1.

11. A nucleic acid molecule encoding AAV-1 helper functions, said molecule comprising an AAV rep coding region and an AAV cap coding region, wherein said rep coding region comprises an AAV-1 rep coding region comprising at least one member selected from the group consisting of:

- (a) rep 78, nt 335 to 2304 of SEQ ID NO: 1;
- (b) rep 68, nt 335 to 2272 of SEQ ID NO: 1 or the c DNA corresponding thereto;
- (c) rep 52, nt 1007 to 2304 of SEQ ID NO: 1; and
- (d) rep 40, nt 1007 to 2272 of SEQ ID NO: 1 or the cDNA corresponding thereto.

14. A host cell stably transduced with an AAV-1 P5 promoter having the sequence of nt 236 to 299 of SEQ ID NO: 1.

16. A pharmaceutical composition comprising a carrier and a virus comprising the vector according to claim 7.

17. A pharmaceutical composition comprising a carrier and a virus comprising the vector according to claim 8.

18. A method for AAV-mediated delivery of a transgene comprising the step of delivering to a host cell an AAV virion which comprises:

(a) a capsid comprising at least one capsid protein encoded by an AAV-1 cap gene; and

(b) a DNA molecule comprising a transgene under the control of regulatory sequences directing its expression.

19. A method for AAV-mediated delivery of a transgene to a host comprising the steps of:

(a) assaying a sample from the host to determine the presence of neutralizing antibodies specific against any serotype of AAV; and

(b) delivering to the host an AAV virion which comprises:

(i) a capsid comprising at least one capsid protein encoded by a cap gene of an AAV serotype against which the host has no antibodies as determined in step (a); and

(ii) a DNA molecule comprising a transgene under the control of regulatory sequences directing its expression.

20. The method according to claim 19, comprising the additional step of repeating steps (a) and (b).

23. A method for producing a selected gene product comprising the steps of transfecting a mammalian cell with the molecule according to claim 1 or a functional fragment thereof and culturing said cell under conditions suitable to express said gene product.

24. The recombinant vector according to claim 3, wherein said vector further comprises AAV-1 capsid proteins having the sequence of SEQ ID NO: 13, 15 or 17 or functional fragments thereof.

25. The recombinant vector according to claim 3, wherein said vector further comprises adenovirus sequences.

26. The host cell transduced with a recombinant viral vector according to claim 3.

27. The host cell transduced with a nucleic acid molecule according to claim 1.

28. The host cell transduced with a nucleic acid molecule according to claim 2.

29. The host cell transduced with a nucleic acid molecule according to claim 10.

30. The host cell transduced with a nucleic acid molecule according to claim 11.

31. The pharmaceutical composition comprising a carrier and a virus comprising the vector according to claim 3.

32. The method for delivery of a transgene comprising the step of delivering to a host cell a recombinant virus comprising a recombinant vector according to claim 3.

ADENO-ASSOCIATED VIRUS SEROTYPE I NUCLEIC ACID
SEQUENCES, VECTORS AND HOST CELLS CONTAINING SAME

This work was supported by the National Institutes of Health, grant no. P30
DK47757-06 and PO1 HD32649-04. The US government may have certain rights in
5 this invention.

Field of the Invention

This invention relates generally to viral vector, and more particularly, to
recombinant viral vectors useful for gene delivery.

Background of the Invention

10 Adeno-associated viruses are small, single-stranded DNA viruses which
require helper virus to facilitate efficient replication [K.I. Berns, *Parvoviridae: the
viruses and their replication*, p. 1007-1041, in F.N. Fields et al., Fundamental
virology, 3rd ed., vol. 2, (Lippencott-Raven Publishers, Philadelphia, PA) (1995)].
The 4.7 kb genome of AAV is characterized by two inverted terminal repeats (ITR)
15 and two open reading frames which encode the Rep proteins and Cap proteins,
respectively. The Rep reading frame encodes four proteins of molecular weight 78
kD, 68 kD, 52 kD and 40 kD. These proteins function mainly in regulating AAV
replication and integration of the AAV into a host cell's chromosomes. The Cap
reading frame encodes three structural proteins in molecular weight 85 kD (VP 1), 72
20 kD (VP2) and 61 kD (VP3) [Berns, cited above]. More than 80% of total proteins in
AAV virion comprise VP3. The two ITRs are the only cis elements essential for AAV
replication, packaging and integration. There are two conformations of AAV ITRs
called "flip" and "flop". These differences in conformation originated from the
replication model of adeno-associated virus which use the ITR to initiate and reinitiate
25 the replication [R.O. Snyder et al., J. Virol., 67:6096-6104 (1993); K.I. Berns,
Microbiological Reviews, 54:316-329 (1990)].

AAVs have been found in many animal species, including primates, canine,
fowl and human [F.A. Murphy et al., "The Classification and Nomenclature of
Viruses: Sixth Report of the International Committee on Taxonomy of Viruses",

Archives of Virology, (Springer-Verlag, Vienna) (1995)]. In addition to five known primate AAVs (AAV-1 to AAV-5), AAV-6, another serotype closely related to AAV-2 and AAV-1 has also been isolated [E. A. Rutledge et al., J. Virol., 72:309-319 (1998)]. Among all known AAV serotypes, AAV-2 is perhaps the most well-
5 characterized serotype, because its infectious clone was the first made [R.J. Samulski et al., Proc. Natl. Acad. Sci. USA, 79:2077-2081 (1982)]. Subsequently, the full sequences for AAV-3A, AAV-3B, AAV-4 and AAV-6 have also been determined [Rutledge, cited above; J.A. Chiorini et al., J. Virol., 71:6823-6833 (1997); S. Muramatsu et al., Virol., 221:208-217 (1996)]. Generally, all AAVs share more than
10 80% homology in nucleotide sequence.

A number of unique properties make AAV a promising vector for human gene therapy [Muzyczka, Current Topics in Microbiology and Immunology, 158:97-129 (1992)]. Unlike other viral vectors, AAVs have not been shown to be associated with any known human disease and are generally not considered pathogenic. Wild type
15 AAV is capable of integrating into host chromosomes in a site specific manner [R. M. Kotin et al., Proc. Natl. Acad. Sci. USA, 87:2211-2215 (1990)- R.J. Samulski, EMBO J., 10(12):3941-3950 (1991)]. Recombinant AAV vectors can integrate into tissue cultured cells in chromosome 19 if the rep proteins are supplied in *trans* [C. Balague et al., J. Virol., 71:3299-3306 (1997); R. T. Surosky et al., J. Virol.,
20 71:7951-7959 (1997)]. The integrated genomes of AAV have been shown to allow long term gene expression in a number of tissues, including, muscle, liver, and brain [K. J. Fisher, Nature Med., 3(3):306-312 (1997); R. O. Snyder et al., Nature Genetics, 16:270-276 (1997); X. Xiao et al., Experimental Neurology, 144:113-124 (1997); Xiao, J. Virol., 70(11):8098-8108 (1996)].

25 AAV-2 has been shown to be present in about 80-90% of the human population. Earlier studies showed that neutralizing antibodies for AAV-2 are prevalent [W. P. Parks et al., J. Virol., 2:716-722 (1970)]. The presence of such antibodies may significantly decrease the usefulness of AAV vectors based on AAV-2 despite its other merits. What are needed in the art are vectors characterized by the

advantages of AAV-2, including those described above, without the disadvantages, including the presence of neutralizing antibodies.

Summary of the Invention

In one aspect, the invention provides an isolated AAV-1 nucleic acid molecule
5 which is selected from among SEQ ID NO: 1, the strand complementary to SEQ ID NO: 1, and cDNA and RNA sequences complementary to SEQ ID NO: 1 and its complementary strand.

In another aspect, the present invention provides AAV ITR sequences, which include the 5' ITR sequences, nt 1 to 143 of SEQ ID NO. 1; the 3' ITR sequences, nt
10 4576 to 4718 of SEQ ID NO: 1, and fragments thereof.

In yet another aspect, the present invention provides a recombinant vector comprising an AAV-1 ITR and a selected transgene. Preferably, the vector comprises both the 5' and 3' AAV-1 ITRs between which the selected transgene is located.

In still another aspect, the invention provides a recombinant vector comprising
15 an AAV-1 P5 promoter having the sequence of nt 236 to 299 of SEQ ID NO: 1 or a functional fragment thereof.

In a further aspect, the present invention provides a nucleic acid molecule encoding an AAV-1 rep coding region and an AAV-1 cap coding region.

In still another aspect, the present invention provides a host cell transduced with a
20 recombinant viral vector of the invention. The invention further provides a host cell stably transduced with an AAV-1 P5 promoter of the invention.

In still a further aspect, the present invention provides a pharmaceutical composition comprising a carrier and a vector of the invention.

In yet another aspect, the present invention provides a method for AAV--
25 mediated delivery of a transgene to a host involving the step of delivering to a selected host a recombinant viral vector comprising a selected transgene under the control of sequences which direct expression thereof and an adeno-associated virus 1 (AAV-1) virion.

In another aspect, the invention provides a method for in vitro production of a selected gene product using a vector of the invention.

Other aspects and advantages of the invention will be readily apparent to one of skill in the art from the detailed description of the invention.

5 Brief Description of the Drawings

Figs 1A-1C illustrate the alignment of nucleotides of AAV-1 [SEQ ID NO: 1], AAV-2 [SEQ ID NO: 18] and AAV-6 [SEQ ID NO: 19]. The alignment was done with MacVector 6.0. The full sequences of AAV-1 are shown in the top line. Nucleotides in AAV-2 and AAV-6 identical to AAV-1 are symbolized by "." and gaps by "-". Some of the conserved features among AAVs are marked in this figure. Note the 3' ITRs of AAV-1 and AAV-6 are shown in different orientations.

Fig. 2 illustrates the predicted secondary structure of AAV-1 ITR. The nucleotides in AAV-2 and AAV-6 are shown in italic and bold respectively.

Fig. 3A illustrates a hypothesis of how AAV-6 arose from the homologous recombination between AAV-1 and AAV-2. The major elements of AAV-1 are indicated in the graph. A region that is shared between AAV-1, AAV-2 and AAV-6 is shown in box with waved lines.

Fig 3B is a detailed illustration of a 71 bp homologous region among AAV-1, AAV-2 and AAV-6. Nucleotides that differ among these serotypes are indicated by arrows.

Fig. 4A is a bar chart illustrating expression levels of human alpha 1 anti-trypsin (α 1AT) in serum following delivery of hAAT via recombinant AAV-1 and recombinant AAV-2 viruses.

Fig. 4B is a bar chart illustrating expression levels of erythropoietin (epo) in serum following delivery of the epo gene via recombinant AAV-1 and recombinant AAV-2 viruses.

Fig. 5A is a bar chart illustrating expression levels of α 1AT in liver following delivery of α 1AT as described in Example 7.

Fig. 5B is a bar chart demonstrating expression levels of epo in liver following delivery of epo as described in Example 7.

Fig. 5C is a bar chart demonstrating neutralizing antibodies (NAB) directed to AAV-1 following delivery of α 1AT or epo to liver as described in Example 7.

5 Fig. 5D is a bar chart demonstrating neutralizing antibodies (NAB) directed to AAV-2 following delivery of α 1AT or epo to liver as described in Example 7.

Fig. 6A is a bar chart illustrating expression levels of α 1AT in muscle following delivery of α 1AT as described in Example 7.

10 Fig. 6B is a bar chart demonstrating expression levels of epo in muscle following delivery of epo as described in Example 7.

Fig. 6C is a bar chart demonstrating neutralizing antibodies (NAB) directed to AAV-1 following delivery of α 1AT or epo to muscle as described in Example 7.

Fig. 6D is a bar chart demonstrating neutralizing antibodies (NAB) directed to AAV-2 following delivery of α 1AT or epo to muscle as described in Example 7.

15 Detailed Description of the Invention

The present invention provides novel nucleic acid sequences for an adeno-- associated virus of serotype 1 (AAV-1). Also provided are fragments of these AAV-1 sequences. Among particularly desirable AAV-1 fragments are the inverted terminal repeat sequences (ITRs), rep and cap. Each of these fragments may be readily
20 utilized, e.g., as a cassette, in a variety of vector systems and host cells. Such fragments may be used alone, in combination with other AAV-1 sequences or fragments, or in combination with elements from other AAV or non-AAV viral sequences. In one particularly desirable embodiment, a cassette may contain the AAV-1 ITRs of the invention flanking a selected transgene. In another desirable
25 embodiment, a cassette may contain the AAV-1 rep and/or cap proteins, e.g., for use in producing recombinant (rAAV) virus.

Thus, the AAV-1 sequences and fragments thereof are useful in production of rAAV, and are also useful as antisense delivery vectors, gene therapy vectors, or vaccine vectors. The invention further provides nucleic acid molecules, gene delivery

vectors, and host cells which contain the AAV-1 sequences of the invention. Also provided a novel methods of gene delivery using AAV vectors.

As described herein, the vectors of the invention containing the AAV-1 capsid proteins of the invention are particularly well suited for use in applications in which the neutralizing antibodies diminish the effectiveness of other AAV serotype based vectors, as well as other viral vectors. The rAAV vectors of the invention are particularly advantageous in rAAV readministration and repeat gene therapy.

These and other embodiments and advantages of the invention are described in more detail below. As used throughout this specification and the claims, the term “comprising” is inclusive of other components, elements, integers, steps and the like.

I. AAV-1 NUCLEIC ACID AND PROTEIN SEQUENCES

The AAV-1 nucleic acid sequences of the invention include the DNA sequences of SEQ ID NO: 1 (Figs. 1A-1C), which consists of 4718 nucleotides. The AAV-1 nucleic acid sequences of the invention further encompass the strand which is complementary to SEQ ID NO: 1, as well as the RNA and cDNA sequences corresponding to SEQ ID NO: 1 and its complementary strand. Also included in the nucleic acid sequences of the invention are natural variants and engineered modifications of SEQ ID NO: 1 and its complementary strand. Such modifications include, for example, labels which are known in the art, methylation, and substitution of one or more of the naturally occurring nucleotides with an analog.

Further included in this invention are nucleic acid sequences which are greater than 85%, preferably at least about 90%, more preferably at least about 95%, and most preferably at least about 98 - 99% identical or homologous to SEQ ID NO:1. The term “percent sequence identity” or “identical” in the context of nucleic acid sequences refers to the residues in the two sequences which are the same when aligned for maximum correspondence. The length of sequence identity comparison may be over the full-length sequence, or a fragment at least about nine nucleotides, usually at least about 20 - 24 nucleotides, at least about 28 - 32 nucleotides, and preferably at least about 36 or more nucleotides. There are a number of different

algorithms known in the art which can be used to measure nucleotide sequence identity. For instance, polynucleotide sequences can be compared using Fasta, a program in GCG Version 6.1. Fasta provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson, 1990, herein incorporated by reference). For instance, percent sequence identity between nucleic acid sequences can be determined using Fasta with its default parameters (a word size of 6 and the NOPAM factor for the scoring matrix) as provided in GCG Version 6.1, herein incorporated by reference.

The term "substantial homology" or "substantial similarity," when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 95 - 99% of the sequence.

Also included within the invention are fragments of SEQ ID NO: 1, its complementary strand, cDNA and RNA complementary thereto. Suitable fragments are at least 15 nucleotides in length, and encompass functional fragments which are of biological interest. Certain of these fragments may be identified by reference to Figs. 1A-1C. Examples of particularly desirable functional fragments include the AAV-1 inverted terminal repeat (ITR) sequences of the invention. In contrast to the 145 nt ITRs of AAV-2, AAV-3, and AAV-4, the AAV-1 ITRs have been found to consist of only 143 nucleotides, yet advantageously are characterized by the T-shaped hairpin structure which is believed to be responsible for the ability of the AAV-2 ITRs to direct site-specific integration. In addition, AAV-1 is unique among other AAV serotypes, in that the 5' and 3' ITRs are identical. The full-length 5' ITR sequences of AAV-1 are provided at nucleotides 1-143 of SEQ ID NO: 1 (Fig. 1A) and the full-length 3' ITR sequences of AAV-1 are provided at nt 4576-4718 of SEQ ID NO: 1 (Fig. 1C). One of skill in the art can readily utilize less than the full-length 5' and/or 3' ITR sequences for various purposes and may construct modified ITRs using conventional techniques, e.g., as described for AAV-2 ITRs in Samulski et al, Cell, 33:135-143 (1983).

Another desirable functional fragment of the AAV-1 genome is the P5 promoter of AAV-1 which has sequences unique among AAV P5 promoters, while maintaining critical regulatory elements and functions. This promoter is located within nt 236 - 299 of SEQ ID NO: 1 (Fig. 1A). Other examples of functional fragments of interest include the sequences at the junction of the rep/cap, e.g., the sequences spanning nt 2306-2223, as well as larger fragments which encompass this junction which may comprise 50 nucleotides on either side of this junction. Still other examples of functional fragments include the sequences encoding the rep proteins. Rep 78 is located in the region of nt 334 - 2306 of SEQ ID NO: 1; Rep 68 is located in the region of nt 334-2272, and contains an intron spanning nt 1924-2220 of SEQ ID NO: 1. Rep 52 is located in the region of nt 1007 - 2304 of SEQ ID NO: 1, rep 40 is located in the region of nt 1007 - 2272, and contains an intron spanning nt 1924-2246 of SEQ ID NO: 1. Also of interest are the sequences encoding the capsid proteins, VP 1 [nt 2223-4431 of SEQ ID NO: 1], VP2 [nt 2634-4432 of SEQ ID NO: 1] and VP3 [nt 2829-4432 of SEQ ID NO: 1]. Other fragments of interest may include the AAV-1 P19 sequences, AAV-1 P40 sequences, the rep binding site, and the terminal resolute site (TRS).

The invention further provides the proteins and fragments thereof which are encoded by the AAV-1 nucleic acids of the invention. Particularly desirable proteins include the rep and cap proteins, which are encoded by the nucleotide sequences identified above. These proteins include rep 78 [SEQ ID NO:5], rep 68 [SEQ ID NO:7], rep 52 [SEQ ID NO:9], rep 40 [SEQ ID NO: 11], vpl [SEQ ID NO: 13], vp2 [SEQ ID NO: 15], and vp3 [SEQ IID NO: 17] and functional fragments thereof while the sequences of the rep and cap proteins have been found to be closely related to those of AAV-6, there are differences in the amino acid sequences (see Table 1 below), as well as differences in the recognition of these proteins by the immune system. However, one of skill in the art may readily select other suitable proteins or protein fragments of biological interest. Suitably, such fragments are at least 8 amino acids in length. However, fragments of other desired lengths may be readily utilized.

Such fragments may be produced recombinantly or by other suitable means, e.g., chemical synthesis.

The sequences, proteins, and fragments of the invention may be produced by any suitable means, including recombinant production, chemical synthesis, or other
5 synthetic means. Such production methods are within the knowledge of those of skill in the art and are not a limitation of the present invention.

II. VIRAL VECTORS

In another aspect, the present invention provides vectors which utilize the AAV-1 sequences of the invention, including fragments thereof, for delivery of a
10 heterologous gene or other nucleic acid sequences to a target cell. Suitably, these heterologous sequences (i.e., a transgene) encode a protein or gene product which is capable of being expressed in the target cell. Such a transgene may be constructed in the form of a "minigene". Such a "minigene" includes selected heterologous gene sequences and the other regulatory elements necessary to transcribe the gene and
15 express the gene product in a host cell. Thus, the gene sequences are operatively linked to regulatory components in a manner which permit their transcription. Such components include conventional regulatory elements necessary to drive expression of the transgene in a cell containing the viral vector. The minigene may also contain a selected promoter which is linked to the transgene and located, with other regulatory
20 elements, within the selected viral sequences of the recombinant vector.

Selection of the promoter is a routine matter and is not a limitation of this invention. Useful promoters may be constitutive promoters or regulated (inducible) promoters, which will enable control of the timing and amount of the transgene to be expressed. For example, desirable promoters include the cytomegalovirus (CMV)
25 immediate early promoter/enhancer [see, e.g., Boshart et al, Cell, 41:521-530 (1985)], the Rous sarcoma virus LTR promoter/enhancer, and the chicken cytoplasmic β -actin promoter [T. A. Kost et al, Nucl. Acids Res., 11(23):8287 (1983)]. Still other desirable promoters are the albumin promoter and an AAV P5 promoter. Optionally, the selected promoter is used in conjunction with a heterologous enhancer, e.g., the β -

actin promoter may be used in conjunction with the CMV enhancer. Yet other suitable or desirable promoters and enhancers may be selected by one of skill in the art.

The minigene may also desirably contain nucleic acid sequences heterologous to the viral vector sequences including sequences providing signals required for efficient polyadenylation of the transcript (poly-A or pA) and introns with functional splice donor and acceptor sites. A common poly-A sequence which is employed in the exemplary vectors of this invention is that derived from the papovavirus SV-40. The poly-A sequence generally is inserted in the minigene downstream of the transgene sequences and upstream of the viral vector sequences. A common intron sequence is also derived from SV-40, and is referred to as the SV40 T intron sequence. A minigene of the present invention may also contain such an intron, desirably located between the promoter/enhancer sequence and the transgene. Selection of these and other common vector elements are conventional [see, e.g., Sambrook et al, "Molecular Cloning. A Laboratory Manual", 2d edit., Cold Spring Harbor Laboratory, New York (1989) and references cited therein] and many such sequences are available from commercial and industrial sources as well as from Genebank.

The selection of the transgene is not a limitation of the present invention. Suitable transgenes may be readily selected from among desirable reporter genes, therapeutic genes, and optionally, genes encoding immunogenic polypeptides. Examples of suitable reporter genes include β -galactosidase (β -gal), an alkaline phosphatase gene, and green fluorescent protein (GFP). Examples of therapeutic genes include, cytokines, growth factors, hormones, and differentiation factors, among others. The transgene may be readily selected by one of skill in the art. See, e.g., WO 98/09657, which identifies other suitable transgenes.

Suitably, the vectors of the invention contain, at a minimum, cassettes which consist of fragments of the AAV-1 sequences and proteins. In one embodiment, a vector of the invention comprises a selected transgene, which is flanked by a 5' ITR and a 3' ITR, at least one of which is an AAV-1 ITR of the invention. Suitably,

vectors of the invention may contain a AAV-1 P5 promoter of the invention. In yet another embodiment, a plasmid or vector of the invention contains AAV-1 rep sequences. In still another embodiment, a plasmid or vector of the invention contains at least one of the AAV-1 cap proteins of the invention. Most suitably, these AAV-1-derived vectors are assembled into viral vectors, as described herein

A. AAV Viral Vectors

In one aspect, the present invention provides a recombinant AAV-1 viral vector produced using the AAV-1 capsid proteins of the invention. The packaged rAAV-1 virions of the invention may contain, in addition to a selected minigene, other AAV-1 sequences, or may contain sequences from other AAV serotypes.

Methods of generating rAAV virions are well known and the selection of a suitable method is not a limitation on the present invention. See, e.g., K. Fisher et al, *J. Virol.*, 70:520-532 (1993) and US Patent 5,478,745. In one suitable method, a selected host cell is provided with the AAV sequence encoding a rep protein, the gene encoding the AAV cap protein and with the sequences for packaging and subsequent delivery. Desirably, the method utilizes the sequences encoding the AAV-1 rep and/or cap proteins of the invention.

In one embodiment, the rep/cap genes and the sequences for delivery are supplied by co-transfection of vectors carrying these genes and sequences. In one currently preferred embodiment, a cis (vector) plasmid, a trans plasmid containing the rep and cap genes, and a plasmid containing the adenovirus helper genes are co-transfected into a suitable cell line, e.g., 293. Alternatively, one or more of these functions may be provided in trans via separate vectors, or may be found in a suitably engineered packaging cell line.

An exemplary cis plasmid will contain, in 5' to 3' order, AAV 5' ITR, the selected transgene, and AAV 3' ITR. In one desirable embodiment, at least one of the AAV ITRs is a 143 nt AAV-1 ITR. However, other AAV serotype ITRs may be readily selected. Suitably, the full-length ITRs are utilized. However, one of skill in

the art can readily prepare modified AAV ITRs using conventional techniques. Similarly, methods for construction of such plasmids is well known to those of skill in the art.

5 A trans plasmid for use in the production of the rAAV-1 virion particle may be prepared according to known techniques. In one desired embodiment, this plasmid contains the rep and cap proteins of AAV-1, or functional fragments thereof. Alternatively, the rep sequences may be from another selected AAV serotype.

The cis and trans plasmid may then be co-transfected with a wild-type helper virus (e.g., Ad2, Ad5, or a herpesvirus), or more desirably, a replication -
10 defective adenovirus, into a selected host cell. Alternatively, the cis and trans plasmid may be co-transfected into a selected host cell together with a transfected plasmid which provides the necessary helper functions. Selection of a suitable host cell is well within the skill of those in the art and include such mammalian cells as 293 cells, HeLa cells, among others.

15 Alternatively, the cis plasmid and, optionally the trans plasmid, may be transfected into a packaging cell line which provides the remaining helper functions necessary for production of a rAAV containing the desired AAV-1 sequences of the invention. An example of a suitable packaging cell line, where an AAV-2 capsid is desired, is B-50, which stably expresses AAV-2 rep and cap genes under the control
20 of a homologous P5 promoter. This cell line is characterized by integration into the cellular chromosome of multiple copies (at least 5 copies) of P5-rep-cap gene cassettes in a concatomer form. This B-50 cell line was deposited with the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209, on September 18, 1997 under Accession No. CRL-12401 pursuant to the
25 provisions of the Budapest Treaty. However, the present invention is not limited as to the selection of the packaging cell line.

Exemplary transducing vectors based on AAV-1 capsid proteins have been tested both *in vivo* and *in vitro*, as described in more detail in Example 4. In these studies, it was demonstrated that recombinant AAV vector with an AAV-1
30 virion can transduce both mouse liver and muscle. These, and other AAV-1 based

gene therapy vectors which may be generated by one of skill in the art are beneficial for gene delivery to selected host cells and gene therapy patients since the neutralization antibodies of AAV-1 present in much of the human population exhibit different patterns from other AAV serotypes and therefore do not neutralize the AAV-1 virions. One of skill in the art may readily prepare other rAAV viral vectors containing the AAV-1 capsid proteins provided herein using a variety of techniques known to those of skill in the art. One may similarly prepare still other rAAV viral vectors containing AAV-1 sequence and AAV capsids of another serotype.

B Other Viral Vectors

One of skill in the art will readily understand that the AAV-1 sequences of the invention can be readily adapted for use in these and other viral vector systems for *in vitro*, *ex vivo* or *in vivo* gene delivery. Particularly well suited for use in such viral vector systems are the AAV-1 ITR sequences, the AAV-1 rep, the AAV-1 cap, and the AAV-1 P5 promoter sequences.

For example, in one desirable embodiment, the AAV-1 ITR sequences of the invention may be used in an expression cassette which includes AAV-1 5' ITR, a non-AAV DNA sequences of interest (e.g., a minigene), and 3' ITR and which lacks functional rep/cap. Such a cassette containing an AAV-1 ITR may be located on a plasmid for subsequent transfection into a desired host cell, such as the cis plasmid described above. This expression cassette may further be provided with an AAV capsid of a selected serotype to permit infection of a cell or stably transfected into a desired host cell for packaging of rAAV virions. Such an expression cassette may be readily adapted for use in other viral systems, including adenovirus systems and lentivirus systems. Methods of producing Ad/AAV vectors are well known to those of skill in the art. One desirable method is described in PCT/US95/14018. However, the present invention is not limited to any particular method.

Another aspect of the present invention is the novel AAV-1 P5 promoter sequences which are located in the region spanning nt 236 - 299 of SEQ ID NO: 1. This promoter is useful in a variety of viral vectors for driving expression of a desired transgene.

Similarly, one of skill in the art can readily select other fragments of the AAV-1 genome of the invention for use in a variety of vector systems. Such vector systems may include, e.g., lentiviruses, retroviruses, poxviruses, vaccinia viruses, and adenoviral systems, among others. Selection of these vector systems is not a
5 limitation of the present invention.

C Host Cells And Packaging Cell Lines

In yet another aspect, the present invention provides host cells which may be transiently transfected with AAV-1 nucleic acid sequences of the invention to permit expression of a desired transgene or production of a rAAV particle. For
10 example, a selected host cell may be transfected with the AAV-1 P5 promoter sequences and/or the AAV-1 5' ITR sequences using conventional techniques. Providing AAV helper functions to the transfected cell lines of the invention results in packaging of the rAAV as infectious rAAV particles. Such cell lines may be produced in accordance with known techniques [see, e.g., US Patent No. 5,658,785], making
15 use of the AAV-1 sequences of the invention.

Alternatively, host cells of the invention may be stably transfected with a rAAV expression cassette of the invention, and with copies of AAV-1 rep and cap genes. Suitable parental cell lines include mammalian cell lines and it may be desirable to select host cells from among non-simian mammalian cells. Examples of suitable
20 parental cell lines include, without limitation, HeLa [ATCC CCL 2], A549 [ATCC Accession No. CCL 185], KB [CCL 17], Detroit [e.g., Detroit 510, CCL 72] and WI-38 [CCL 75] cells. These cell lines are all available from the American Type Culture Collection, 10801 University Boulevard, Manassas, Virginia 20110-2209 USA. Other suitable parent cell lines may be obtained from other sources and may be used to
25 construct stable cell lines containing the P5 and/or AAV rep and cap sequences of the invention.

Recombinant vectors generated as described above are useful for delivery of the DNA of interest to cells.

III. METHODS OF DELIVERING GENES VIA AAV-1 DERIVED VECTORS

In another aspect, the present invention provides a method for delivery of a transgene to a host which involves transfecting or infecting a selected host cell with a recombinant viral vector generated with the AAV-1 sequences (or functional fragments thereof) of the invention. Methods for delivery are well known to those of skill in the art and are not a limitation of the present invention.

In one desirable embodiment, the invention provides a method for AAV--mediated delivery of a transgene to a host. This method involves transfecting or infecting a selected host cell with a recombinant viral vector containing a selected transgene under the control of sequences which direct expression thereof and AAV-1 capsid proteins.

Optionally, a sample from the host may be first assayed for the presence of antibodies to a selected AAV serotype. A variety of assay formats for detecting neutralizing antibodies are well known to those of skill in the art. The selection of such an assay is not a limitation of the present invention. See, e.g., Fisher et al, Nature Med., 3(3):306-312 (March 1997) and W. C. Manning et al, Human Gene Therapy, 9:477-485 (March 1, 1998). The results of this assay may be used to determine which AAV vector containing capsid proteins of a particular serotype are preferred for delivery, e.g., by the absence of neutralizing antibodies specific for that capsid serotype.

In one aspect of this method, the delivery of vector with AAV-1 capsid proteins may precede or follow delivery of a gene via a vector with a different serotype AAV capsid protein. Thus, gene delivery via rAAV vectors may be used for repeat gene delivery to a selected host cell. Desirably, subsequently administered rAAV vectors carry the same transgene as the first rAAV vector, but the subsequently administered vectors contain capsid proteins of serotypes which differ from the first vector. For example, if a first vector has AAV-2 capsid proteins, subsequently administered vectors may have capsid proteins selected from among the other serotypes, including AAV-1, AAV-3A, AAV-3B, AAV-4 and AAV-6.

Thus, a rAAV-1-derived recombinant viral vector of the invention provides an efficient gene transfer vehicle which can deliver a selected transgene to a selected host cell *in vivo or ex vivo* even where the organism has neutralizing antibodies to one or more AAV serotypes. These compositions are particularly well suited to gene
5 delivery for therapeutic purposes. However, the compositions of the invention may also be useful in immunization. Further, the compositions of the invention may also be used for production of a desired gene product *in vitro*.

The above-described recombinant vectors may be delivered to host cells according to published methods. An AAV viral vector bearing the selected transgene
10 may be administered to a patient, preferably suspended in a biologically compatible solution or pharmaceutically acceptable delivery vehicle. A suitable vehicle includes sterile saline. Other aqueous and non-aqueous isotonic sterile injection solutions and aqueous and non-aqueous sterile suspensions known to be pharmaceutically acceptable carriers and well known to those of skill in the art may be employed for
15 this purpose.

The viral vectors are administered in sufficient amounts to transfect the cells and to provide sufficient levels of gene transfer and expression to provide a therapeutic benefit without undue adverse effects, or with medically acceptable physiological effects, which can be determined by those skilled in the medical arts.
20 Conventional and pharmaceutically acceptable routes of administration include, but are not limited to, direct delivery to the liver, oral, intranasal, intravenous, intramuscular, subcutaneous, intradermal, and other parental routes of administration. Routes of administration may be combined, if desired.

Dosages of the viral vector will depend primarily on factors such as the
25 condition being treated, the age, weight and health of the patient, and may thus vary among patients. For example, a therapeutically effective human dosage of the viral vector is generally in the range of from about 1 ml to about 100 ml of solution containing concentrations of from about 1×10^9 to 1×10^{16} genomes virus vector. A preferred human dosage may be about 1×10^{13} to 1×10^{16} AAV genomes. The
30 dosage will be adjusted to balance the therapeutic benefit against any side effects and

such dosages may vary depending upon the therapeutic application for which the recombinant vector is employed. The levels of expression of the transgene can be monitored to determine the frequency of dosage resulting in viral vectors, preferably AAV vectors containing the minigene. Optionally, dosage regimens similar to those described for therapeutic purposes may be utilized for immunization using the compositions of the invention. For *in vitro* production, a desired protein may be obtained from a desired culture following transfection of host cells with a rAAV containing the gene encoding the desired protein and culturing the cell culture under conditions which permits expression. The expressed protein may then be purified and isolated, as desired. Suitable techniques for transfection, cell culturing, purification, and isolation are known to those of skill in the art.

The following examples illustrate several aspects and embodiments of the invention.

Example 1 - Generation of Infectious Clone of AAV-1

The replicated form DNA of AAV-1 was extracted from 293 cells that were infected by AAV-1 and wild type adenovirus type 5.

A. Cell Culture and Virus

AAV-free 293 cells and 84-31 cells were provided by the human application laboratory of the University of Pennsylvania. These cells were cultured in Dulbecco's Modified Eagle Medium with 10% fetal bovine serum (Hyclone), penicillin (100 U/ml) and streptomycin at 37°C in a moisturized environment supplied with 5% CO₂. The 84-31 cell line constitutively expresses adenovirus genes E1a, E1b, E4/ORF6, and has been described previously [K. J. Fisher, *J. Virol.*, **70**:520-532 (1996)]. AAV-1 (ATCC VR-645) seed stock was purchased from American Type Culture Collection (ATCC, Manassas, VA). AAV viruses were propagated in 293 cells with wild type Ad5 as a helper virus.

B. Recombinant AAV Generation

The recombinant AAV viruses were generated by transfection using an adenovirus free method. Briefly, the cis plasmid (with AAV ITR), trans plasmid (with

AAV rep gene and cap gene) and helper plasmid (pF Δ 13, with essential regions from the adenovirus genome) were simultaneously co-transfected into 293 cells in a ratio of 1:1:2 by calcium phosphate precipitation. The pF Δ 13 helper plasmid has an 8 kb deletion in the adenovirus E2B region and has deletions in most of the late genes.

5 This helper plasmid was generated by deleting the RsrII fragment from pFG140 (Microbix, Canada). Typically, 50 μ g of DNA (cis:trans:PF Δ 13 at ratios of 1:1:2, respectively) was transfected onto a 15 cm tissue culture dish. The cells were harvested 96 hours post-transfection, sonicated and treated with 0.5% sodium deoxycholate (37°C for 10 min). Cell lysates were then subjected to two rounds of a
10 CsCl gradient. Peak fractions containing AAV vector were collected, pooled, and dialyzed against PBS before injecting into animals. To make rAAV virus with AAV-1 virion, the pAV1H or p5E18 (2/1) was used as the *trans* plasmid to provide rep and cap function.

For the generation of rAAV based on AAV-2, p5E18 was used as the
15 *trans* plasmid since it greatly improved the rAAV yield. This plasmid, p5E18(2/2), expresses AAV-2 Rep and Cap and contains a P5 promoter relocated to a position 3' to the Cap gene, thereby minimizing expression of Rep78 and Rep68. The strategy was initially described by Li et al, J. Virol., 71:5236-5243 (1997). P5E18(2/2) was constructed in the following way. The previously described pMMTV-*trans* vector
20 (i.e., the mouse mammary tumor virus promoter substituted for the P5 promoter in an AAV-2-based vector) was digested with *Sma*I and *Cla*I, filled in with the Klenow enzyme, and then recircularized with DNA ligase. The resulting construct was digested with *Xba*I, filled in, and ligated to the blunt-ended BamHI-*Xba*I fragment from pCR-p5, constructed in the following way. The P5 promoter of AAV was
25 amplified by PCR and the amplified fragment was subsequently cloned into pCR2.1 (Invitrogen) to yield pCR-P5. The helper plasmid pAV1H was constructed by cloning the *Bfa*I fragment of pAAV-2 into pBluescript II-SK(+) at the *Bco*rV and *Sma*I sites. The 3.0-kb *Xba*I-*Kpn*I fragment from p5E18(2/2), the 2.3-kb *Xba*I-*Kpn*I fragment from pAV1H, and the 1.7-kb *Kpn*I fragment from p5E18(2/2) were incorporated into
30 a separate plasmid P5E18(2/1), which contains AAV-2 Rep, AAV-1 Cap, and the

AAV-2 P5 promoter located 3' to the Cap gene. Plasmid p5E18(2/1) produced 10- to 20-fold higher quantities of the vector than pAV1H (i.e., 10^{12} genomes/50 15-cm² plates).

C. DNA Techniques

5 Hirt DNA extraction was performed as described in the art with minor modification [R.J. Samulski et al., Cell, 33:135-143 (1983)]. More particularly, Hirt solution without SDS was used instead of using original Hirt solution containing SDS. The amount of SDS present in the original Hirt solution was added after the cells had been fully suspended. To construct AAV-1 infectious clone, the Hirt DNA from
10 AAV-1 infected 293 cells was repaired with Klenow enzyme (New England Biolabs) to ensure the ends were blunt. The treated AAV-1 Hirt DNA was then digested with *Bam*HI and cloned into three vectors, respectively. The internal *Bam*HI was cloned into pBlueScript II-SK+ cut with *Bam*HI to get pAV1-BM. The left and right fragments were cloned into pBlueScript II-SK+ cut with *Bam*HI + EcoRV to obtain
15 pAV1-BL and pAV1-BR, respectively. The AAV sequence in these three plasmids were subsequently assembled into the same vector to get AAV-1 infectious clone pAAV-1. The helper plasmid for recombinant AAV-1 virus generation was constructed by cloning the Bfa I fragment of pAAV-1 into pBlueScript II-SK+ at the EcoRV site.

20 Analysis of the Hirt DNA revealed three bands, a dimer at 9.4 kb, a monomer at 4.7 kb and single-stranded DNA at 1.7 kb, which correlated to different replication forms of AAV-1. The monomer band was excised from the gel and then digested with *Bam*HI. This resulted in three fragments of 1.1 kb, 0.8 kb and 2.8 kb. This pattern is in accordance with the description by Bantel-schaal and zur Hausen,
25 Virol., 134(1):52-63 (1984). The 1.1 kb and 2.8 kb *Bam*HI fragments were cloned into pBlueScript-KS(+) at *Bam*HI and EcoRV site. The internal 0.8 kb fragment was cloned into *Bam*HI site of pBlueScript-KS(+).

These three fragments were then subcloned into the same construct to obtain a plasmid (pAAV-1) that contained the full sequence of AAV-1. The pAAV-1
30 was then tested for its ability to rescue from the plasmid backbone and package

infectious virus. The pAAV-1 was then transfected to 293 cells and supplied with adenovirus type as helper at MOI 10. The virus supernatant was used to reinfect 293 cells.

For Southern blot analysis, Hirt DNA was digested with *DpnI* to
5 remove bacteria-borne plasmid and probed with internal *BamHI* fragment of AAV-1. The membrane was then washed at high stringency conditions, which included: twice 30 minutes with 2X SSC, 0.1% SDS at 65°C and twice 30 minutes with 0.1X SSC, 0.1% SDS at 65°C. The membrane was then analyzed by both phosphor image and X-ray autoradiography. The results confirmed that pAAV-1 is indeed an infectious
10 clone of AAV serotype 1.

Example 2 - Sequencing Analysis of AAV-1

The entire AAV-1 genome was then determined by automatic sequencing and was found to be 4718 nucleotides in length (Figs. 1A-1C). For sequencing, an ABI 373 automatic sequencer as used to determine the sequences for all plasmids and PCR
15 fragments related to this study using the FS dye chemistry. All sequences were confirmed by sequencing both plus and minus strands. These sequences were also confirmed by sequencing two independent clones of pAV-BM, pAV-BL and pAV-BR. Since the replicated form of AAV-1 DNA served as the template for sequence determination, these sequences were also confirmed by sequencing a series of PCR
20 products using original AAV-1 seed stock as a template.

The length of AAV-1 was found to be within the range of the other serotypes: AAV-3 (4726 nucleotides), AAV-4 (4774 nucleotides), AAV-2 (4681 nucleotides), and AAV-6 (4683 nucleotides).

The AAV-1 genome exhibited similarities to other serotypes of adeno-
25 associated viruses. Overall, it shares more than 80% identity with other known AAV viruses as determined by the computer program Megalign using default settings [DNASTAR, Madison, WI]. The key features in AAV-2 can also be found in AAV-1. First, AAV-1 has the same type of inverted terminal repeat which is capable of forming T-shaped hairpin structures, despite the differences at the nucleotide level

(Figs. 2 and 3). The sequences of right ITRs and left ITRs of AAV-1 are identical. The AAV TR sequence is subdivided into A, A', B, B', C, C', D and D' [Bern, cited above].

These AAV ITR sequences are also virtually the same as those found in AAV-6 right ITR, there being one nucleotide difference in each of A and A' sequence, and the last nucleotide of the D sequence. Second, the AAV-2 rep binding motif [GCTCGCTCGCTCGCTG (SEQ ID NO: 20)] is well conserved. Such motif can also be found in the human chromosome 19 AAV-2 pre-integration region. Finally, non-structural and structural coding regions, and regulatory elements similar to those of other AAV serotypes also exist in AAV-1 genome.

Although the overall features of AAV terminal repeats are very much conserved, the total length of the AAV terminal repeat exhibits divergence. The terminal repeat of AAV-1 consists of 143 nucleotides while those of AAV-2, AAV-3, and AAV-4 are about 145 or 146 nucleotides. The loop region of AAV-1 ITR most closely resembles that of AAV-4 in that it also uses TCT instead of the TTT found in AAV-2 and AAV-3. The possibility of sequencing error was eliminated using restriction enzyme digestion, since these three nucleotides are part of the SacI site (gagctc, nt 69-74 of SEQ ID NO: 1). The p5 promoter region of AAV-1 shows more variations in nucleotide sequences with other AAV serotypes. However, it still maintains the critical regulatory elements. The two copies of YY1 [See, Fig. 1A-1C] sites seemed to be preserved in all known AAV serotypes, which have been shown to be involved in regulating AAV gene expression. In AAV-4, there are 56 additional nucleotides inserted between YY1 and E-box/USF site, while in AAV-1, there are 26 additional nucleotides inserted before the E-box/USF site. The p19 promoter, p40 promoter and polyA can also be identified from the AAV-1 genome by analogy to known AAV serotypes, which are also highly conserved.

Thus, the analysis of AAV terminal repeats of various serotypes showed that the A and A' sequence is very much conserved. One of the reasons may be the Rep binding motif (GCTC)₃GCTG [SEQ ID NO: 20]. These sequences appear to be essential for AAV DNA replication and site-specific integration. The same sequence

has also been shown to be preserved in a monkey genome [Samulski, personal communication]. The first 8 nucleotides of the D sequence are also identical in all known AAV serotypes. This is in accordance with the observation of the Srivastava group that only the first 10 nucleotides are essential for AAV packaging [X.S. Wang et al, J. Virol., 71:3077-3082 (1997); X.S. Wang et al, J. Virol., 71:1140-1146 (1997)]. The function of the rest of the D sequences still remain unclear. They may be somehow related to their tissue specificities. The variation of nucleotide in B and C sequence may also suggest that the secondary structure of the ITRs is more critical for its biological function, which has been demonstrated in many previous publications.

Example 3 - Comparison of AAV-1 Sequences

The nucleotide sequences of AAV-1, obtained as described above, were compared with known AAV sequences, including AAV-2, AAV-4 and AAV-6 using DNA Star Megalign. This comparison revealed a stretch of 71 identical nucleotides shared by AAV-1, AAV-2 and AAV-6. See, Figs. 1A-1C.

This comparison further suggested that AAV-6 is a hybrid formed by homologous recombination of AAV-1 and AAV-2. See, Figs. 3A and 3B. These nucleotides divide the AAV-6 genome into two regions. The 5' half of AAV-6 of 522 nucleotides is identical to that of AAV-2 except in 2 positions. The 3' half of AAV-6 including the majority of the rep gene, complete cap gene and 3' ITR is 98% identical to AAV-1.

Biologically, such recombination may enable AAV-1 to acquire the ability to transmit through the human population. It is also interesting to note that the ITRs of AAV-6 comprise one AAV-1 ITR and one AAV-2 ITR. The replication model of defective parvovirus can maintain this special arrangement. Studies on AAV integration have shown that a majority of AAV integrants carries deletions in at least one of the terminal repeats. These deletions have been shown to be able to be repaired through gene conversion using the other intact terminal repeat as a template. Therefore, it would be very difficult to maintain AAV-6 as a homogenous population

when an integrated copy of AAV-6 is rescued from host cells with helper virus infection. The AAV-6 with two identical AAV-2 ITRs or two identical AAV-1 ITRs should be the dominant variants. The AAV-6 with two AAV-1 ITRs has been observed by Russell's group [Rutledge, cited above (1998)]. So far there is no report on AAV-6 with two AAV-2 ITRs. Acquisition of AAV-2 P5 promoter by AAV-6 may have explained that AAV-6 have been isolated from human origin while AAV-1 with the same virion has not. The regulation of P5 promoter between different species of AAV may be different *in vivo*. This observation suggests the capsid proteins of AAV were not the only determinants for tissue specificity.

Although it is clear that AAV-6 is a hybrid of AAV-1 and AAV-2, AAV-6 has already exhibited divergence from either AAV-1 or AAV-2. There are two nucleotide differences between AAV-6 and AAV-2 in their first 450 nucleotides. There are about 1% differences between AAV-6 and AAV-1 in nucleotide levels from nucleotides 522 to the 3' end. There also exists a quite divergent region (nucleotide 4486-4593) between AAV-6 and AAV-1 (Figs. 1A-1C). This region does not encode any known proteins for AAVs. These differences in nucleotide sequences may suggest that AAV-6 and AAV-1 have gone through some evolution since the recombination took place. Another possible explanation is that there exists another variant of AAV-1 which has yet to be identified. So far, there is no evidence to rule out either possibility. It is still unknown if other hybrids (AAV-2 to AAV-4, etc.) existed in nature.

The coding region of AAV-1 was deduced by comparison with other known AAV serotypes. Table 1 illustrates the coding region differences between AAV-1 and AAV-6. The amino acid residues are deduced according to AAV-2.

With reference to the amino acid position of AAV-1, Table 1 lists the amino acids of AAV-1 which have been changed to the corresponding ones of AAV-6. The amino acids of AAV-1 are shown to the left of the arrow. Reference may be made to SEQ ID NO: 5 of the amino acid sequence of AAV-1 Rep 78 and to SEQ ID NO: 13 for the amino acid sequence of AAV-1 VP1.

Table 1

Coding region variations between AAV-1 and AAV-6

Rep protein (Rep78)			Cap protein (VP1)	
Position(s)	Amino acids		Position(s)	Amino acids
28	S→N		129	L→F
191	Q→H		418	E→D
192	H→D		531	E→K
308	E→D		584	F→L
			598	A→V
			642	N→H

It was surprising to see that the sequence of the AAV-1 coding region is almost identical to that of AAV-6 from position 452 to the end of coding region (99%). The first 508 nucleotides of AAV-6 have been shown to be identical to those of AAV-2 [Rutledge, cited above (1998)]. Since the components of AAV-6 genome seemed to be AAV-2 left ITR – AAV-2 p5 promoter – AAV-1 coding region – AAV-1 right ITR, it was concluded that AAV-6 is a naturally occurred hybrid between AAV-1 and AAV-2.

Example 4 - Gene Therapy Vector Based on AAV-1

Recombinant gene transfer vectors based on AAV-1 viruses were constructed by the methods described in Example 1. To produce a hybrid recombinant virus with AAV-1 virion and AAV-2 ITR, the AAV-1 trans plasmid (pAV1H) and the AAV-2 cis-lacZ plasmid (with AAV-2 ITR) were used. The AAV-2 ITR was used in this vector in view of its known ability to direct site-specific integration. Also constructed for use in this experiment was an AAV-1 vector carrying the green fluorescent protein (GFP) marker gene under the control of the immediate early promoter of CMV using pAV1H as the trans plasmid.

A. rAAV-1 Viruses Transfect Host Cells in Vitro

84-31 cells, which are subclones of 293 cells (which express adenovirus E1a, E1b) which stably express E4/ORF5, were infected with rAAV-1 GFP or rAAV-lacZ. High levels of expression of GFP and lacZ was detected in the
5 cultured 84-31 cells. This suggested that rAAV-1 based vector was very similar to AAV-2 based vectors in ability to infect and expression levels.

B. rAAV-1 Viruses Transfect Cells in Vivo

The performance of AAV-1 based vectors was also tested *in vivo*. The rAAV-1 CMV- α 1AT virus was constructed as follows. The EcoRI fragment of
10 pAT85 (ATCC) containing human α 1-antitrypsin (α 1AT) cDNA fragment was blunted and cloned into PCR (Promega) at a SmaI site to obtain PCR- α 1AT. The CMV promoter was cloned into PCR- α 1AT at the XbaI site. The Alb- α 1AT expression cassette was removed by XhoI and ClaI and cloned into pAV1H at the XbaI site. This vector plasmid was used to generate AAV-1-CMV- α 1AT virus used
15 in the experiment described below.

For screening human antibodies against AAV, purified AAV virus is lysed with Ripa buffer (10 mM Tris pH 8.2, 1% Triton X-100, 1% SDS, 0.15 M NaCl) and separated in 10% SDS-PAGE gel. The heat inactivated human serum was used at a 1 to 1000 dilution in this assay. The rAAV-1 CMV- α 1AT viruses were
20 injected into Rag-1 mice through tail vein injection at different dosages. The concentration of human α 1-antitrypsin in mouse serum was measured using ELISA. The coating antibody is rabbit anti-human human α 1-antitrypsin (Sigma). The goat-antihuman α 1-antitrypsin (Sigma) was used as the primary detection antibodies. The sensitivity of this assay is around 0.3 ng/ml to 30 ng/ml. The expression of human α -
25 antitrypsin in mouse blood can be detected in a very encouraging level. This result is shown in Table 2.

Table 2

Human Antitrypsin Expressed in Mouse Liver

Amount of virus injected	Week 2 (ng/ml)	Week 4 (ng/ml)
2x10 ¹⁰ genomes	214.2	171.4
1x10 ¹⁰ genomes	117.8	109.8
5x10 ¹⁰ genomes	64.5	67.8
2.5x10 ¹⁰ genomes	30.9	58.4

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rAAV-1 CMV-lacZ viruses were also injected into the muscle of C57BL6 mice and similar results were obtained. Collectively, these results suggested that AAV-1 based vector would be appropriate for both liver and muscle gene delivery.

Example 5 - Neutralizing Antibodies Against AAV-1

Simple and quantitative assays for neutralizing antibodies (NAB) to AAV-1 and AAV-2 were developed with recombinant vectors. A total of 33 rhesus monkeys and 77 normal human subjects were screened.

A. Nonhuman Primates

Wild-caught juvenile rhesus monkeys were purchased from Covance (Alice, Tex.) and LABS of Virginia (Yemassee, SC) and kept in full quarantine. The monkeys weighed approximately 3 to 4 kg. The nonhuman primates used in the Institute for Human Gene Therapy research program are purposefully bred in the United States from specific-pathogen-free closed colonies. All vendors are US Department of Agriculture class A dealers. The rhesus macaques are therefore not infected with important simian pathogens, including the tuberculosis agent, major simian lentiviruses (simian immunodeficiency virus and simian retroviruses), and cercopithecine herpesvirus. The animals are also free of internal and external parasites. The excellent health status of these premium animals minimized the potential for extraneous variables. For this study, serum was obtained from monkeys prior to initiation of any protocol.

NAB titers were analyzed by assessing the ability of serum antibody to inhibit the transduction of reporter virus expressing green fluorescent protein (GFP) (AAV1-GFP or AAV2-GFP) into 84-31 cells. Various dilutions of antibodies preincubated with reporter virus for 1 hour at 37°C were added to 90% confluent cell
5 cultures. Cells were incubated for 48 hours and the expression of green fluorescent protein was measured by FluoroImaging (Molecular Dynamics). NAB titers were calculated as the highest dilution at which 50% of the cells stained green.

Analysis of NAB in rhesus monkeys showed that 61% of animals tested positive for AAV-1; a minority (24%) has NAB to AAV-2. Over one-third of
10 animals had antibodies to AAV-1 but not AAV-2 (i.e., were monospecific for AAV-1), whereas no animals were positive for AAV-2 without reacting to AAV-1. These data support the hypothesis that AAV-1 is endemic in rhesus monkeys. The presence of true AAV-2 infections in this group of nonhuman primates is less clear, since cross-neutralizing activity of an AAV-1 response to AAV-2 can not be ruled out. It is
15 interesting that there is a linear relationship between AAV-2 NAB and AAV-1 NAB in animals that had both.

B. *Humans*

For these neutralization antibody assays, human serum samples were incubated at 56°C for 30 min to inactivate complement and then diluted in DMEM.
20 The virus (rAAV or rAd with either lacZ or GFP) was then mixed with each serum dilution (20X, 400X, 2000X, 4000X, etc.) and incubated for 1 hour at 37°C before applied to 90% confluent cultures of 84-31 cells (for AAV) or Hela cells (for adenovirus) in 96-well plates. After 60 minutes of incubation at culture condition, 100 µl additional media containing 20% FCS was added to make final culture media
25 containing 10% FCS.

The result is summarized in Table 3.

Table 3

Adenovirus	AAV-1	AAV-2	# of samples	Percentage
-	-	-	41	53.2%
+	-	-	16	20.8%
-	+	-	0	0.0%
-	-	+	2	2.6%
-	+	+	2	2.6%
+	-	+	3	3.9%
+	+	-	0	0.0%
+	+	+	13	16.9%
Total			77	100%

The human neutralizing antibodies against these three viruses seemed to be unrelated since the existence of neutralizing antibodies against AAV are not indications for antibodies against adenovirus. However, AAV requires adenovirus as helper virus, in most of the cases, the neutralizing antibodies against AAV correlated with the existence of neutralizing antibodies to adenovirus. Among the 77 human serum samples screened, 41% of the samples can neutralize the infectivity of recombinant adenovirus based on Ad5. 15/77 (19%) of serum samples can neutralize the transduction of rAAV-1 while 20/77 (20%) of the samples inhibit rAAV-2 transduction at 1 to 80 dilutions or higher. All serum samples positive in neutralizing antibodies for AAV-1 in are also positive for AAV-2. However, there are five (6%) rAAV-2 positive samples that failed to neutralize rAAV-1. In samples that are positive for neutralizing antibodies, the titer of antibodies also varied in the positive ones. The results from screening human sera for antibodies against AAVs supported the conclusion that AAV-1 presents the same epitome as that of AAV-2 to interact

with cellular receptors since AAV-1 neutralizing human serums can also decrease the infectivity of AAV-2. However, the profile of neutralizing antibodies for these AAVs is not identical, there are additional specific receptors for each AAV serotype.

Example 6 - Recombinant AAV Viruses Exhibit Tissue Tropism

5 The recombinant AAV-1 vectors of the invention and the recombinant AAV-2 vectors [containing the gene encoding human α 1-antitrypsin (α 1AT) or murine erythropoietin (Epo) from a cytomegalovirus-enhanced β -actin promoter (CB)] were evaluated in a direct comparison to equivalent copies of AAV-2 vectors containing the same vector genes.

10 Recombinant viruses with AAV-1 capsids were constructed using the techniques in Example 1. To make rAAV with AAV-1 virions, pAV1H or p5E18 (2/1) was used as the *trans* plasmid to provide Rep and Cap functions. For the generation of the rAAV based on AAV-2, p5E18(2/2) was used as the *trans* plasmid, since it greatly improved the rAAV yield. [Early experiments indicated similar *in vivo* performances of AAV-1 vectors produced with pAV1H and p5E19 (2/1). All subsequent studies used AAV-1 vectors derived from p5E18(2/1) because of the increased yield.]

15 Equivalent stocks of the AAV-1 and AAV-2 vectors were injected intramuscularly (5×10^{10} genomes) or liver via the portal circulation (1×10^{11} genomes) into immunodeficient mice, and the animals (four groups) were analyzed on day 30 for expression of transgene. See, Figs. 4A and 4B.

20 AAV-2 vectors consistently produced 10- to 50-fold more serum erythropoietin or α 1-antitrypsin when injected into liver compared to muscle. (However, the AAV-1-delivered genes did achieve acceptable expression levels in the liver.) This result was very different from that for AAV-1 vectors, with which muscle expression was equivalent to or greater than liver expression. In fact, AAV-1 outperformed AAV-2 in muscle when equivalent titers based on genomes were administered.

Example 7 - Gene Delivery via rAAV-1

C57BL/6 mice (6- to 8-week old males, Jackson Laboratories) were analyzed for AAV mediated gene transfer to liver following intrasplenic injection of vector (i.e., targeted to liver). A total of 10^{11} genome equivalents of rAAV-1 or rAAV-2 vector
5 were injected into the circulation in 100 μ l buffered saline. The first vector contained either an AAV-1 capsid or an AAV-2 capsid and expressed α 1AT under the control of the chicken β -actin (CB) promoter. Day 28 sera were analyzed for antibodies against AAV-1 or AAV-2 and serum α 1AT levels were checked. Animals were then injected with an AAV-1 or AAV-2 construct expressing erythropoietin (Epo, also under the
10 control of the CB promoter). One month later sera was analyzed for serum levels of Epo. The following groups were analyzed (Figs. 5A-5D).

In Group 1, vector 1 was AAV-2 expressing α 1AT and vector 2 was AAV-2 expressing Epo. Animals generated antibodies against AAV-2 following the first vector administration which prevented the readministration of the AAV-2 based
15 vector. There was no evidence for cross-neutralizing the antibody to AAV-1.

In Group 2, vector 1 was AAV-1 expressing α 1AT while vector 2 was AAV-1 expressing Epo. The first vector administration did result in significant α 1AT expression at one month associated with antibodies to neutralizing antibodies to AAV-1. The animals were not successfully readministered with the AAV-1 Epo
20 expressing construct.

In Group 3, the effectiveness of an AAV-2 vector expressing Epo injected into a naive animal was measured. The animals were injected with PBS and injected with AAV-2 Epo vector at day 28 and analyzed for Epo expression one month later. The neutralizing antibodies were evaluated at day 28 so we did not expect to see anything
25 since they received PBS with the first vector injection. This shows that in naive animals AAV-2 is very efficient at transferring the Epo gene as demonstrated by high level of serum Epo one month later.

Group 4 was an experiment similar to Group 3 in which the animals originally received PBS for vector 1 and then the AAV-1 expressing Epo construct 28 days
30 later. At the time of vector injection, there obviously were no antibodies to either

AAV-1 or AAV-2. The AAV-1 based vector was capable of generating significant expression of Epo when measured one month later.

Group 5 is a cross-over experiment where the initial vector is AAV-2 expressing α 1AT followed by the AAV-1 construct expressing Epo. The animals, as expected, were efficiently infected with the AAV-2 vector expressing α 1AT as shown by high levels of the protein in blood at 28 days. This was associated with significant neutralizing antibodies to AAV-2. Importantly, the animals were successfully administered AAV-1 following the AAV-2 vector as shown by the presence of Epo in serum 28 days following the second vector administration. At the time of this vector administration, there was high level AAV-2 neutralizing antibodies and very low cross-reaction to AAV-1. The level of Epo was slightly diminished possibly due to a small amount of cross-reactivity. Group 6 was the opposite cross-over experiment in which the initial vector was AAV-1 based, whereas the second experiment was AAV-2 based. The AAV-1 vector did lead to significant gene expression of α 1AT, which also resulted in high level AAV-1 neutralizing antibody. The animals were very efficiently administered AAV-2 following the initial AAV-1 vector as evidenced by high level Epo.

A substantially identical experiment was performed in muscle in which 5×10^{10} genomes were injected into the tibialis anterior of C57BL/6 mice as a model for muscle directed gene therapy. The results are illustrated in Figs. 6A-6D and are essentially the same as for liver.

In summary, this experiment demonstrates the utility of using an AAV-1 vector in patients who have pre-existing antibodies to AAV-2 or who had initially received an AAV-2 vector and need readministration.

25 Example 8 - Construction of Recombinant Viruses Containing AAV-1 ITRs

This example illustrates the construction of recombinant AAV vectors which contain AAV-1 ITRs of the invention.

An AAV-1 cis plasmid is constructed as follows. A 160 bp Xho-NruI AAV-1 fragment containing the AAV-1 5' ITR is obtained from pAV1-BL. pAV1-BL was

generated as described in Example 1. The Xho-NruI fragment is then cloned into a second pAV1-BL plasmid at an XbaI site to provide the plasmid with two AAV-1 ITRs. The desired transgene is then cloned into the modified pAV-1BL at the NruI and BamHI site, which is located between the AAV-1 ITR sequences. The resulting
5 AAV-1 cis plasmid contains AAV-1 ITRs flanking the transgene and lacks functional AAV-1 rep and cap.

Recombinant AAV is produced by simultaneously transfecting three plasmids into 293 cells. These include the AAV-1 cis plasmid described above; a trans plasmid which provides AAV rep/cap functions and lacks AAV ITRs; and a plasmid providing
10 adenovirus helper functions. The rep and/or cap functions may be provided in trans by AAV-1 or another AAV serotype, depending on the immunity profile of the intended recipient. Alternatively, the rep or cap functions may be provided in cis by AAV-1 or another serotype, again depending on the patient's immunity profile.

In a typical cotransfection, 50 µg of DNA (cis:trans:helper at ratios of 1:1:2, respectively) is transfected onto a 15 cm tissue culture dish. Cells are harvested 96
15 hours post transfection, sonicated and treated with 0.5% sodium deoxycholate (37° for 10 min). Cell lysates are then subjected to 2-3 rounds of ultracentrifugation in a cesium gradient. Peak fractions containing rAAV are collected, pooled and dialyzed against PBS. A typical yield is 1×10^{13} genomes/ 10^9 cells.

20 Using this method, one recombinant virus construct is prepared which contains the AAV-1 ITRs flanking the transgene, with an AAV-1 capsid. Another recombinant virus construct is prepared with contains the AAV-1 ITRs flanking the transgene, with an AAV-2 capsid.

All publications cited in this specification are incorporated herein by reference.
25 While the invention has been described with reference to a particularly preferred embodiments, it will be appreciated that modifications can be made without departing from the spirit of the invention. Such modifications are intended to fall within the scope of the claims.

What is claimed is.

1. An isolated AAV-1 nucleic acid molecule comprising a sequence selected from the group consisting of:
 - (a) SEQ ID NO: 1;
 - (b) a DNA sequence complementary to SEQ ID NO: 1;
 - (c) cDNA complementary to (a) or (b); and
 - (d) RNA complementary to any of (a) to (c).
2. A nucleic acid molecule comprising an AAV-1 inverted terminal repeat (ITR) sequence selected from the group consisting of:
 - (a) nt 1 to 143 of SEQ ID NO: 1;
 - (b) nt 4576 to 4718 of SEQ ID NO: 1;
 - (c) a nucleic acid sequence complementary to (a) or (b); and
 - (d) a functional fragment of (a), (b), or (c).
3. A recombinant vector comprising a 5' AAV-1 inverted terminal repeat (ITR) and a selected transgene, wherein said ITR has the sequence selected from the group consisting of:
 - (a) nt 1 to 143 of SEQ ID NO: 1;
 - (b) a nucleic acid sequence complementary to (a); and
 - (c) a functional fragment of (a) or (b).
4. The recombinant vector according to claim 3, wherein said vector further comprises a 3' AAV-1 ITR.

5. A recombinant vector comprising a 3' AAV-1 inverted terminal repeat (ITR) and a selected transgene, wherein said ITR has the sequence selected from the group consisting of:

- (a) nt 4576 to 4718 of SEQ ID NO: 1;
- (b) a nucleic acid sequence complementary to (a); and
- (c) a functional fragment of (a) or (b).

6. The recombinant vector according to claim 5, wherein said vector further comprises a 5' AAV-1 ITR.

7. The recombinant vector according to any of claims 3-6, wherein said vector further comprises AAV-1 capsid proteins having the sequence of SEQ ID NO: 13, 15 or 17 or functional fragments thereof.

8. The recombinant vector according to any of claims 3-6, wherein said vector further comprises adenovirus sequences.

9. A recombinant vector comprising an AAV-1 P5 promoter having the sequence of nt 236 to 299 of SEQ ID NO: 1 or a functional fragment thereof.

10. A nucleic acid molecule encoding AAV-1 helper functions, said molecule comprising an AAV rep coding region and an AAV cap coding region, wherein said cap coding region comprises at least one member is selected from the group consisting of:

- (a) vp1, nt 2223 to 4431 of SEQ ID NO: 1;
- (b) vp2, nt 2634 to 4432 of SEQ ID NO: 1; and
- (c) vp3, nt 2829 to 4432 of SEQ ID NO: 1.

11. A nucleic acid molecule encoding AAV-1 helper functions, said molecule comprising an AAV rep coding region and an AAV cap coding region, wherein said rep coding region comprises an AAV-1 rep coding region comprising at least one member selected from the group consisting of:

- (a) rep 78, nt 335 to 2304 of SEQ ID NO: 1;
- (b) rep 68, nt 335 to 2272 of SEQ ID NO: 1 or the cDNA corresponding thereto,
- (c) rep 52, nt 1007 to 2304 of SEQ ID NO: 1; and
- (d) rep 40, nt 1007 to 2272 of SEQ ID NO: 1 or the cDNA corresponding thereto.

12. A host cell transduced with a recombinant viral vector according to any of claims 3-6.

13. A host cell transduced with a nucleic acid molecule according to any of claims 1, 2, 10 or 11.

14. A host cell stably transduced with an AAV-1 P5 promoter having the sequence of nt 236 to 299 of SEQ ID NO: 1.

15. A pharmaceutical composition comprising a carrier and a virus comprising the vector according to any of claims 3-6.

16. A pharmaceutical composition comprising a carrier and a virus comprising the vector according to claim 7.

17. A pharmaceutical composition comprising a carrier and a virus comprising the vector according to claim 8.

18. A method for AAV-mediated delivery of a transgene comprising the step of delivering to a host cell an AAV virion which comprises:

- (a) a capsid comprising at least one capsid protein encoded by an AAV-1 cap gene; and
- (b) a DNA molecule comprising a transgene under the control of regulatory sequences directing its expression.

19. A method for AAV-mediated delivery of a transgene to a host comprising the steps of:

- (a) assaying a sample from the host to determine the presence of neutralizing antibodies specific against any serotype of AAV; and
- (b) delivering to the host an AAV virion which comprises:
 - (i) a capsid comprising at least one capsid protein encoded by a cap gene of an AAV serotype against which the host has no antibodies as determined in step (a); and
 - (ii) a DNA molecule comprising a transgene under the control of regulatory sequences directing its expression.

20. The method according to claim 19, comprising the additional step of repeating steps (a) and (b).

21. Use of an AAV virion which comprises a capsid comprising (a) at least one capsid protein encoded by a cap gene of an AAV serotype against which the host has antibodies, and (b) a DNA molecule comprising a transgene operably linked to regulatory sequences directing its expression,

in the preparation of a medicament for delivery of a transgene to a host, wherein said host has no preexisting neutralizing antibodies against the AAV serotype of said cap gene.

22. A method for delivery of a transgene comprising the step of delivering to a host cell a recombinant virus comprising a recombinant vector according to any of claims 3-8.

23. A method for producing a selected gene product comprising the steps of transfecting a mammalian cell with the molecule according to claim 1 or a functional fragment thereof and culturing said cell under conditions suitable to express said gene product.

ABSTRACT OF THE DISCLOSURE

The nucleic acid sequences of adeno-associated virus (AAV) serotype 1 are provided, as are vectors and host cells containing these sequences and functional fragments thereof. Also provided are methods of delivering genes via AAV-1 derived
5 vectors.

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FIG 1A

AAV-1	ttgcccactccctctctgcgcgctcgctcgctcggtggggcctgcggaacaaaggtccgc	60
AAV-2	...g.....ac..a....g.gc.....gc.	60
AAV-6	...g.....ac..a....g.gc.....gc.	60
Rep binding site		
AAV-1	agacggcagagctctgctctgcccggcccaccgagcgagcgagcgcgagagagggagtg	120
AAV-2	c....c.c.g...t...c.g.g.....t..gt.....	120
AAV-6	c....c.c.g...t...c.g.g.....t..gt.....	120
TRS		
AAV-1	ggcaactccatcactaggggtaaTCGCGAAGCGCCTCCACGCTGCCGCGTCAGCGCTGA	180
AAV-2	.c.....--..ct.G..G.-----TG.A...G----	163
AAV-6	.c.....--..ct.G..G.-----TG.A...G----	163
E box/USF		
AAV-1	CGTAAATTACGTCATAGGG---GAGTGGTCCTGTATTAGCTGTCACGTGAGTGCTTTTGC	237
AAV-2	...G.....TTA.G.A.....AG.....-	222
AAV-6	...G.....TTA.G.A.....AG.....-	222
YY1 P5/TATA		
AAV-1	GACATTTTGCGACACCACGTGGCCATTTAGGGTATATATGGCCGAGTGAGCGAGCAGGAT	297
AAV-2T....T..CGCT.....T..A.C.....AC.....G.	282
AAV-6T....T..CGCT.....T..A.C.....AC.....G.	282
YY1/p5 RNA Rep 78/68		
AAV-1	CTCCATTTTGAC-CGCGAAATTTGAACGAGCAGCCATGCCGGGCTTCTACGAGATCG	356
AAV-2AG..G..GG.....C.....C.....G..T.....T.	342
AAV-6AG..G..GG.....C.....-.....G..T.....T.	341
AAV-1	TGATCAAGGTGCCGAGCGACCTGGACGAGCACCTGCCGGGCATTTCTGACTCGTTTGTGA	416
AAV-2T.....C..C.....T....G...T.....C.....AGC.....	402
AAV-6T.....C..C.....T.....T.....C.....AGC.....	401
AAV-1	GCTGGGTGGCCGAGAAGGAATGGGAGCTGCCCCCGGATTCTGACATGGATCTGAATCTGA	476
AAV-2	A.....T....G..A.....	462
AAV-6	A.....T....G..A.....	461
AAV-1	TTGAGCAGGCACCCCTGACCGTGGCCGAGAAGCTGCAGCGCGACTTCCTGGTCCAATGGC	536
AAV-2T...ACGG.....	522
AAV-6G.....	521
AAV-1	GCCGCGTGAGTAAGGCCCCGGAGGCCCTCTTCTTTGTTTCAGTTCGAGAAGGGCGAGTCCT	596
AAV-2T.....T.....G..A..T.....A...AG..	582
AAV-6	581
AAV-1	ACTTCCACCTCCATATTCTGGTGGAGACCACGGGGGTCAAATCCATGGTGCTGGGCGCGCT	656
AAV-2A.G..CG.G..C.....A.....C.....G.....TT....A..T.	642
AAV-6	641
AAV-1	TCCTGAGTCAGATTAGGGACAAGCTGGTGCAGACCATCTACCGCGGGATCGAGCCGACCC	716
AAV-2C.C..A..A...A.T....GA..T.....TT	702
AAV-6	701
AAV-1	TGCCCAACTGGTTCGCGGTGACCAAGACGCGTAATGGCGCCGGAGGGGGGAACAAGGTGG	776
AAV-2A.....C..A.....CA.A.....C.....	762
AAV-6	761

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FIG 1B

AAV-1	TGGACGAGTGCTACATCCCCAACTACCTCCTGCCCAAGACTCAGCCCGAGCTGCAGTGGG	836
AAV-2T.....T...T.G..C.....A..C.....T.....C.....	822
AAV-6	821
P19/TATA		P19 RNA
AAV-1	CGTGGACTAACATGGAGGAGTATATAAGCGCCTGTTTGAACCTGGCCGAGCGCAAACGGC	896
AAV-2T.....AC.....T.....C.....G..T..CA.G.....T.....T	882
AAV-6C.....GG.....A.....G.....A..C..GG.C.....	881
AAV-1	TCGTGGCGCAGCACCTGACCCACGTCAGCCAGACCCAGGAGCAGAACAAGGAGAATCTGA	956
AAV-2	.G.....T.....G.....GTCG.....G.....A.....A..	942
AAV-6CG.....	941
		Rep 52/40
AAV-1	ACCCCAATTCTGACGCGCCTGTCATCCGGTCAAAAACCTCCGCGCGCTACATGGAGCTGG	1016
AAV-2	.T.....T.....G..G...A.A.....T..A..CA.G.....	1002
AAV-6A.....	1001
AAV-1	TCGGGTGGCTGGTGGACCGGGGCATCACCTCCGAGAAGCAGTGGATCCAGGAGGACCAGG	1076
AAV-2C.....AA...G..T....G.....	1062
AAV-6	1061
AAV-1	CCTCGTACATCTCCTTCAACGCCGCTTCCAACCTCGCGGTCCCAGATCAAGGCCGCTCTGG	1136
AAV-2A.....T..G..C.....A.....T..CT...	1122
AAV-6	1121
AAV-1	ACAATGCCGGCAAGATCATGGCGCTGACCAAATCCGCGCCCGACTACCTGGTAGGCCCCG	1196
AAV-2G..A.....T...AGC.....T...A....C.....G....AGC	1182
AAV-6	1181
AAV-1	CTCCGCCCCGCGGACATTAAACCAACCGCATCTACCGCATCCTGGAGCTGAACGGCTACG	1256
AAV-2	AG..CGTG.A.....TCC.G...T..G..T..TAAA..TT....A..A.....G....	1242
AAV-6C.....T.....	1241
AAV-1	AACCTGCCTACGCCGGCTCCGTCTTTCTCGGCTGGGCCCAGAAAAGGTTTCGGGAAGCGCA	1316
AAV-2	.T..CCAA..T..G.CT.....G..A.....AC.....A.....C...A.G.	1302
AAV-6	.C.....A..A....	1301
AAV-1	ACACCATCTGGCTGTTTGGGCGGCCACCACGGGCAAGACCAACATCGCGGAAGCCATCG	1376
AAV-2T..A..T..C..G.....G....A.	1362
AAV-6	1361
AAV-1	CCCACGCCGTGCCCTTCTACGGCTGCGTCAACTGGACCAATGAGAACTTTCCCTTCAATG	1436
AAV-2A.T.....G.....A.....C.	1422
AAV-6C.	1421
AAV-1	ATTGCGTCGACAAGATGGTGATCTGGTGGGAGGAGGGCAAGATGACGGCCAAGGTCGTGG	1496
AAV-2	.C..T.....G.....C.....	1482
AAV-6	1481
AAV-1	AGTCCGCCAAGGCCATTCTCGGCGGCAGCAAGGTGCGCGTGGACCAAAAGTGCAAGTCGT	1556
AAV-2G....A.....A..A.....G..A.....C.	1542
AAV-6	1541
AAV-1	CCGCCCAGATCGACCCCAACCCCGTGATCGTCACTCCAACACCAACATGTGCGCCGTGA	1616
AAV-2	.G.....A.....G..T.....	1602
AAV-6T.....	1601

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FIG 1C

AAV-1	TTGACGGGAACAGCACCACCTTCGAGCACCAGCAGCCGTTGCAGGACCGGATGTTCAAAT	1676
AAV-2TCA..G.....A.....A.....	1662
AAV-6	1661
AAV-1	TTGAACTCACCCGCCGTCTGGAGCATGACTTTGGCAAGGTGACAAAGCAGGAAGTCAAAG	1740
AAV-2T.....G.....C..C.....	1722
AAV-6	1721
AAV-1	AGTTCTTCCGCTGGGCGCAGGATCACGTGACCGAGGTGGCGCATGAGTTCTACGTCAGAA	1796
AAV-2	.C..T.....G.....AA.....GTT.....A.....A.....A..	1782
AAV-6	1781
P40/TATA		
AAV-1	AGGGTGGAGCCAACAAAAGACCCGCCCCCGATGACGCGGATAAAAGCGAGCCCAAGCGGG	1856
AAV-2G.....AG.....A...T...T.....A....	1842
AAV-6G.....	1841
P40 RNA		
AAV-1	CCTGCCCTCAGTCGCGGATCCATCGACGTCAGACGCGGAAGGAGCTCCGGTGGACTTTG	1916
AAV-2	TGC..GAG.....T...C.G.....---..T..A.CA...AC.	1899
AAV-6	1901
▼		
AAV-1	CCGACAGGTACCAAAACAAATGTTCTCGTCACGCGGGCATGCTTCAGATGCTGTTTCCCT	1976
AAV-2	.A.....T.....AA..T.....	1959
AAV-6	1961
AAV-1	GCAAGACATGCGAGAGAATGAATCAGAATTTCAACATTTGCTTCACGCACGGGACGAGAG	2036
AAV-2	...GACA.....CA..T..C.....T....ACA..A..	2019
AAV-6	...A.....C....	2021
AAV-1	ACTGTTTCAGAGTGCTTCCCCGGCGTGTGAGAATCTCAACCGGTC---GTCAGAAAGAGGA	2093
AAV-2T.....T...---.....C..TTCT...GTC..A.A.G	2076
AAV-6A..T.....---.....	2078
AAV-1	CGTATCGGAAACTCTGTGCCATTTCATCATCTGCTGGGGCGGGCTCCCGAGATTGCTTGCT	2153
AAV-2A.....G..CTA.....A.CA....AAA..TG..A...---C.....A	2133
AAV-6	2138
Rep 78 stop		
AAV-1	CGGCCTGCGATCTGGTCAACGTGGACCTGGATGACTGTGTTTCTGAGCAATAAATGACTT	2213
AAV-2	.T.....T.....TT.....CA.C.T...A.....T..	2193
AAV-6T.....	2193
▽ VP1		
AAV-1	AAACCAGGTATGGCTGCCGATGGTTATCTTCCAGATTGGCTCGAGGACAACCTCTCTGAG	2273
AAV-2	...T.....CT.....A	2253
AAV-6AC.....G	2258
Rep 68 stop		
AAV-1	GGCATTTCGCGAGTGGTGGGACTTGAAACCTGGAGCCCCGAAGCCCCAAAGCCAACCAGCAA	2333
AAV-2	..A..AA.AC.....A.GC.C.....CC.A..ACCA..A..GC..GCAG...GG	2313
AAV-6A.....	2318
AAV-1	AAGCAGGACGACGGCCGGGTCTGGTGCTTCCTGGCTACAAGTACCTCGGACCCTTCAAC	2393
AAV-2	C.TA.....A..A.....T.....G.....	2373
AAV-6G..C.....G.....C.....	2378

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FIG 1D

AAV-1	GGACTCGACAAGGGGGAGCCCGTCAACGCGGCGGACGCAGCGGCCCTCGAGCACGACAAG	2453
AAV-2A.....G.....A..A.....C.....A	2433
AAV-6T.....	2438
AAV-1	GCCTACGACCAGCAGCTCAAAGCGGGTGACAATCCGTACCTGCGGTATAACCACGCCGAC	2513
AAV-2G.....G.CAGC..A.....C.....CAA...C.....	2493
AAV-6A.AGCG..T.....T.....GCG...T.....	2498
AAV-1	GCCGAGTTTCAGGAGCGTCTGCAAGAAGATACGTCTTTTGGGGGCAACCTCGGGCGAGCA	2573
AAV-2	..G.....C..TA.....A.....	2553
AAV-6	..C.....T..GC.....G.....	2558
AAV-1	GTCTTCCAGGCCAAGAAGCGGGTTCTCGAACCTCTCGGTCTGGTTGAGGAAGGCGCTAAG	2633
AAV-2G..A..A.....T.....G..C.....CCT.T....	2613
AAV-6A.....T.T.....T.....	2618
<u>VP2</u>		
AAV-1	ACGGCTCCTGGAAAGAAACGTCCGGTAGAGCAGTCGCCACAAGAGCCAGACTCCTCCTCG	2693
AAV-2G.....A..GA.G.....C..T..TGTG.....	2673
AAV-6T.....G..AC.T.....G..G..ACAA.....	2678
AAV-1	GGCATCGGCAAGACAGGCCAGCAGCCCGCTAAAAAGAGACTCAATTTTGGTCAGACTGGC	2753
AAV-2	..A.C...A..G.G.....T..A.G...A...T.G.....A	2733
AAV-6T.....	2738
AAV-1	GA CTCAGAGTCAGTCCCCGATCCACAACCTCTCGGAGAACCTCCAGCAACCCCCGCTGCT	2813
AAV-2	...G....C.....A..T..C..C..G.....C.G..A.....G.....T...G.	2793
AAV-6	...T....G....C..C..C..A..A.....G.A..T.....A.....G.....	2798
<u>VP3</u>		
AAV-1	GTGGGACCTACTACAATGGCTTCAGGCGGTGGCGCACCAATGGCAGACAATAACGAAGGC	2873
AAV-2	C.....A...A..G.....A.....A.....G...	2853
AAV-6	2858
AAV-1	GCCGACGGAGTGGGTAATGCCTCAGGAAATTGGCATTGCGATTCCACATGGCTGGGCGAC	2933
AAV-2T....C.....A.....	2913
AAV-6	2918
AAV-1	AGAGTCATCACCACCAGCACCCGCACCTGGGCCTTGCCACCTACAATAACCACCTCTAC	2993
AAV-2A.....C.....C.....	2973
AAV-6A..A.....T..C.....	2978
AAV-1	AAGCAAATCTCCAGTGCTTCAACGGGGGCCAGCAACGACAACCACTACTTCGGCTACAGC	3053
AAV-2	..A.....T.....CCAA...---..A...TCG.....T.....T.....	3030
AAV-6	3038
AAV-1	ACCCCTGGGGGTATTTTGATTTC AACAGATTCCACTGCCACTTTTCACCACGTGACTGG	3113
AAV-2T.....C.....	3090
AAV-6T..C.....	3098
AAV-1	CAGCGACTCATCAACAACAATTGGGGATTCCGGCCCAAGAGACTCAACTTCAAACCTCTTC	3173
AAV-2	..AA.....C.....A.....G.....T	3150
AAV-6G.....	3158
AAV-1	AACATCCAAGTCAAGGAGGTCACGACGAATGATGGCGTCACAACCATCGCTAATAACCTT	3233
AAV-2T.....A.....CA.....C..TACG..G..G..T..C.....	3210
AAV-6G.....	3218

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FIG 1E

AAV-1 ACCAGCACGGTTCAAGTCTTCTCGGACTCGGAGTACCAGCTTCCGTACGTCCTCGGCTCT 3293
AAV-2G..G..TA.T.....C.....G 3270
AAV-6T.G..... 3278

AAV-1 GCGCACCAGGGCTGCCTCCCTCCGTTCCCGGCGGACGTGTTTCATGATTCCGCAATACGGC 3353
AAV-2T..A..A.....G.....A..A.....C.....G.G..A..G..T..A 3330
AAV-6G..... 3338

AAV-1 TACCTGACGCTCAACAATGGCAGCCAGCCGTGGGACGTTTCATCCTTTTACTGCCTGGAA 3413
AAV-2C..C..G.....C..G..T..G..A..A.....C..T..A.....G 3390
AAV-6A.....G..A.....G..... 3398

AAV-1 TATTTCCCTTCTCAGATGCTGAGACGGGCAACAACCTTTACCTTCAGCTACACCTTTGAG 3473
AAV-2 ..C..T.....C.T..C..A.....T..... 3450
AAV-6A..G.....T.....C... 3458

AAV-1 GAAGTGCCTTTCCACAGCAGCTACGCGCACAGCCAGAGCCTGGACCGGCTGATGAATCCT 3533
AAV-2 ..C..T.....T.....T.....T..C..... 3510
AAV-6 ..C..... 3498

AAV-1 CTCATCGACCAATACCTGTATTACCTGAACAGAACTCAAATCAGTCCGGAAGTGCCCAA 3593
AAV-2G.....T...G.....AA.C.C..CAAGT....CCA..ACG 3570
AAV-6G.....G..... 3578

AAV-1 AACAAGGACTTGCTGTTTAGCCGTGGGTCTCCAGCTGGCATGTCTGTTTCAGCCCAAAAAC 3653
AAV-2 C.GTCAAGGC.T.A....TCT.AG.CCGGAG.GAG..A...TCGG.AC...T.T.GG... 3630
AAV-6G..... 3638

AAV-1 TGGCTACCTGGACCCTGTTATCGGCAGCAGCGGTTTCTAAAACAAAAACAGACAACAAC 3713
AAV-2T.....C..C.....A..A.CA..G...TCTG.G..T..... 3690
AAV-6C..... 3698

AAV-1 AACAGCAATTTTACCTGGACTGGTGCTTCAAATATAACCTCAATGGGCGTGAATCCATC 3773
AAV-2TG.A.ACT.G.....A...A.C..G..CC.....CA.A..C..TC.G 3750
AAV-6C.....T.....T..A 3758

AAV-1 ATCAACCCTGGCACTGCTATGGCCTCACACAAAGACGACGAAGACAAGTTCTTTCCCATG 3833
AAV-2 G.G..T..G..GC.C..C.....AAGC.....G.....T....A.....T....TCA. 3810
AAV-6A..... 3818

AAV-1 AGCGGTGTCATGATTTTTGGAAAAGAGAGCGCCGGAGCTTCAAACACTGCATTGGACAAT 3893
AAV-2G..TC.C..C.....G..GC.AG..T.A.AGAAAA....TGTGAACA.T..A..G 3870
AAV-6G..... 3878

AAV-1 GTCATGATTACAGACGAAGAGGAAATTAAAGCCACTAACCCTGTGGCCACCGAAAGATTT 3953
AAV-2CGG.A.A..C..T..C.....T..G..GCAG.A. 3930
AAV-6C.....C.....C..... 3938

AAV-1 GGGACCGTGGCAGTCAATTTCCAGAGCAGCAGCACAGACCCTGCGACCGGAGATGTGCAT 4013
AAV-2 ..TT.T..AT.TAC...CC.....AG...A..G.C.AG.A..T....C.....CA.C 3990
AAV-6T.....C..... 3998

AAV-1 GCTATGGGAGCATTACCTGGCATGGTGTGGCAAGATAGAGACGTGTACCTGCAGGGTCCC 4073
AAV-2 A.ACAA..C.TTC.T..A.....C.....G..C.....T.....T.....G... 4050
AAV-6 T.....C.....A.....C.....A.....T 4058

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FIG 1F

AAV-1 ATTTGGGCCAAAATTCCTCACACAGATGGACACTTTCACCCGTCTCCTCTTATGGGCGGC 4133
 AAV-2 ..C.....A..G.....A.....G..C.....T.....C.....C..C.....T..A 4110
 AAV-6G.....C..... 4118

AAV-1 TTTGGACTCAAGAACCCGCCTCCTCAGATCCTCATCAAAAACACGCCTGTTCTGCGAAT 4193
 AAV-2 ..C.....T..AC....T.....A.....T.....G.....C..G..A..... 4170
 AAV-6T...C..... 4178

AAV-1 CCTCCGGCGGAGTTTTCAGCTACAAAGTTTGCTTCATTTCATCACCCAATACTCCACAGGA 4253
 AAV-2 ...T..A.CACC..CAGT..GG.....C.....A..G.....G... 4230
 AAV-6A.....G.....G..T..... 4238

AAV-1 CA-AGTGAGTGTGGAAATTGAATGGGAGCTGCAGAAAGAAAACAGCAAGCGCTGGAATCC 4312
 AAV-2 ..CG..C..C.....G..C..G.....G.....A..... 4290
 AAV-6 ..-.....C.....G.....A..... 4297

AAV-1 CGAAGTGCAGTACACATCCAATTATGCAAAATCTGCCAA-CGTTGATTTTACTGTGGACA 4371
 AAV-2A.T.....T.....C..CAAC..G....TT..T...G..C.....C.....T. 4350
 AAV-6T.....T..C.....-.....C..... 4356

AAV-1 ACAATGGACTTTTATACTGAGCCTCGCCCCATTGGCACCCGTTACCTTACCCGTCCCCTGT 4431
 AAV-2 CT.....CG.G...T.A.....A.A.....G..T...AAT.... 4410
 AAV-6C..... 4416

VP1-3 stop PolyA signal

AAV-1 AATTACGTGTTAATCAATAAACCGGTTGATTTCGTTTCAGTTGAACTTTGGTCTCCTGTCC 4491
 AAV-2G.T.....T..A.....TGCGTA 4470
 AAV-6GT.....A.....G.....A...G 4476

AAV-1 TTCTTATCTTATC-GGTTACCATGGTTAT-AGCTTACACATTA--ACTGCTTGGTTGCGC 4547
 AAV-2 ..TC.T.....TA...T.....C..CGTAGA..AGT.GC.TGG.G.G..AA.CATTA 4530
 AAV-6 ..A.....T...C.....A.CA.C-C.G.....--.....A..... 4533

AAV-1 TTCGCGATAAAAGACTTACGTCATCGGGttacccttagtgatggagttgcccactccctc 4607
 AAV-2 ACTA.A.gg.a-----g..... 4570
 AAV-6at.----- 4572

AAV-1 tctgcgcgctcgctcgctcggtggggccggcagagcagagctctgccgtctgcggacctt 4667
 AAV-2 .c.....ac..a.....gc..c..a..g..gc...a.gc.c.gg... 4630
 AAV-6 .a.....g..... 4632

AAV-1 tgggtccgcaggccccaccgagcgcgagcgcgcgagagggagtgggcaa 4718
 AAV-2 ..cc.g.gc....t..gt.....c... 4681
 AAV-6t..... 4683

AAV-1 TR

A A
 A A
 G C
 G C
 T A
 C G
 gC Gc
 cG Cg
 C G
 aA Tg a ca
 G CCGGGTGGCTCGCTCGCTCGCGCGTCTCTCCCTCACCCTT
 A C GGCCCCACCGAGCGAGCGCGCAGAGAGGGAGTGGGCAACTCCATCACTAGGGGTAA
 G C t gt
 cG Cg
 C G
 cA Tg
 G C
 gA Tc
 G C
 C G
 T T
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 a g
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FIG 2

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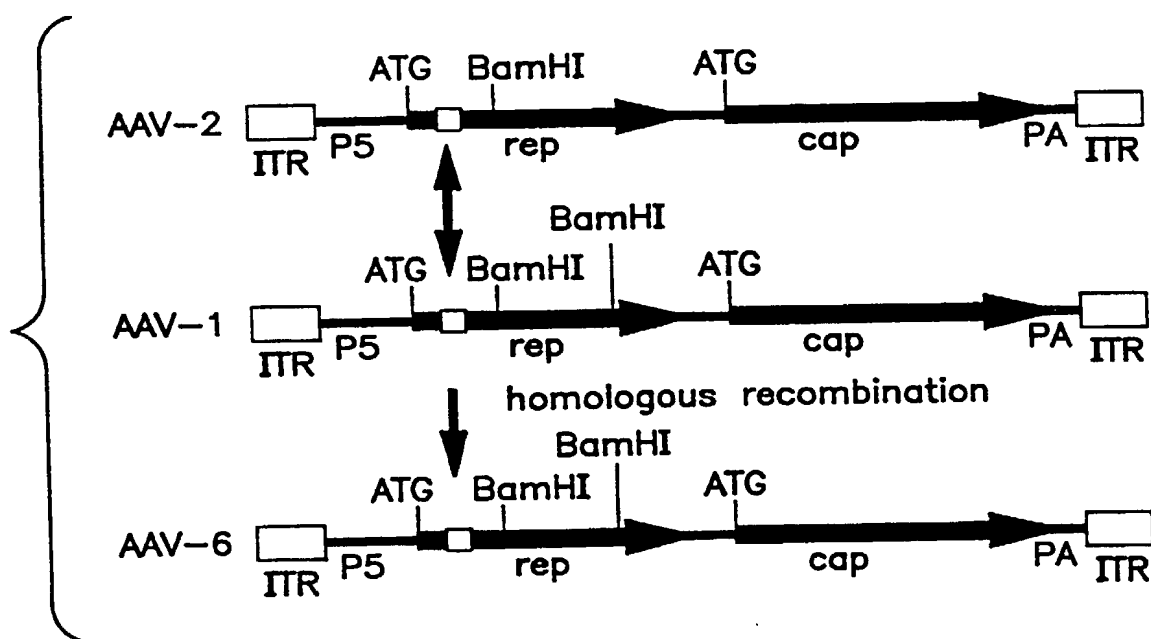


FIG. 3A

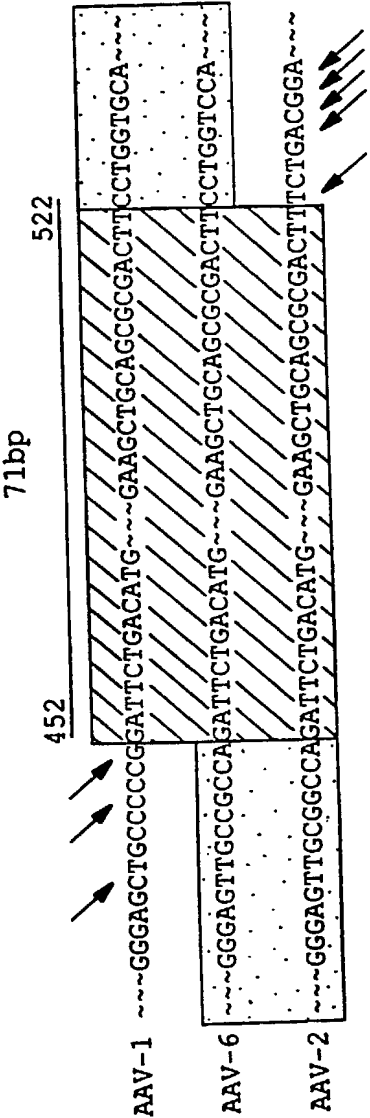


FIG. 3B

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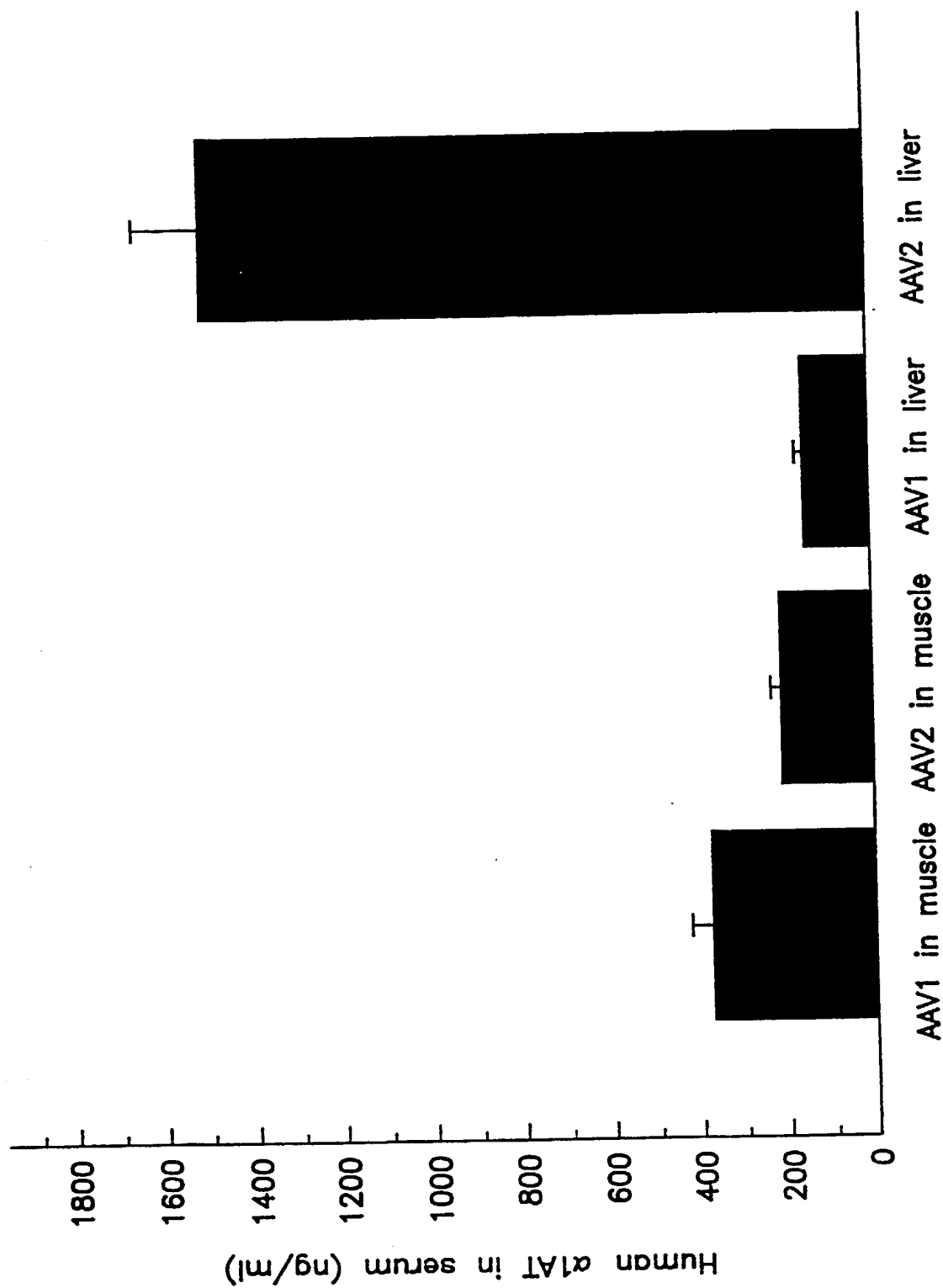


FIG. 4A

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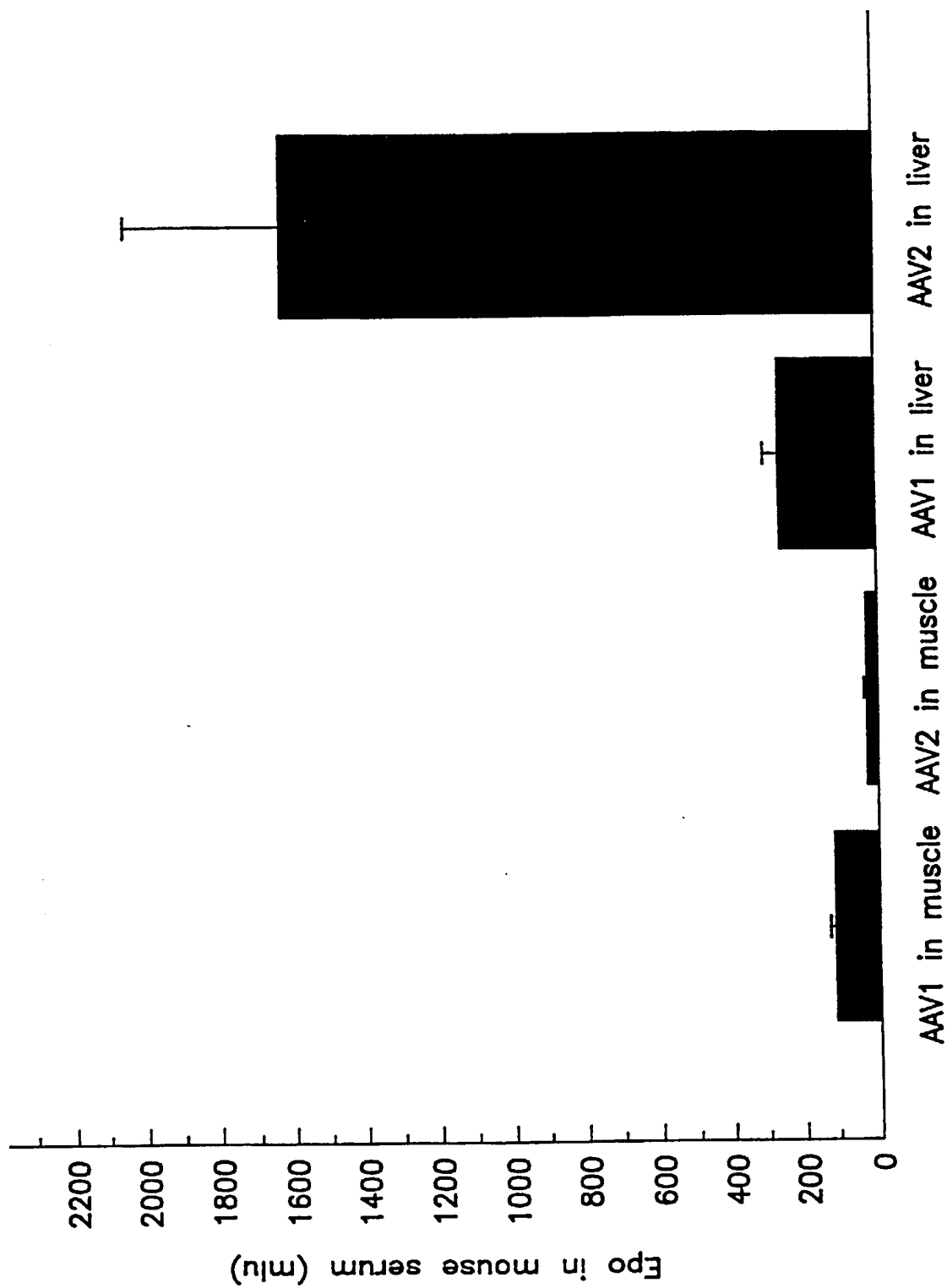


FIG. 4B

FIG. 5A

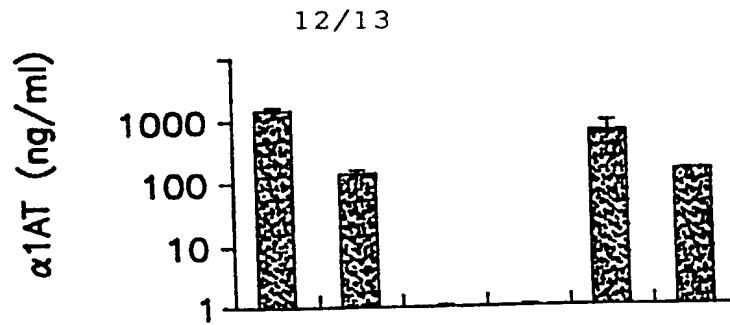


FIG. 5B

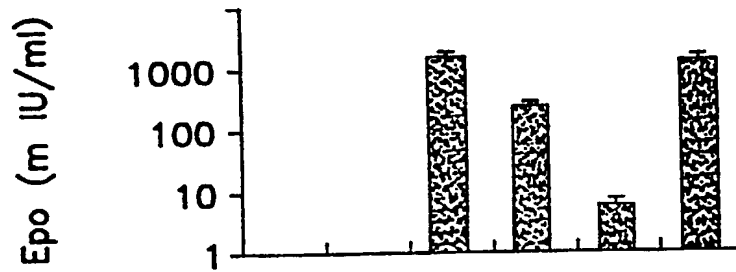


FIG. 5C

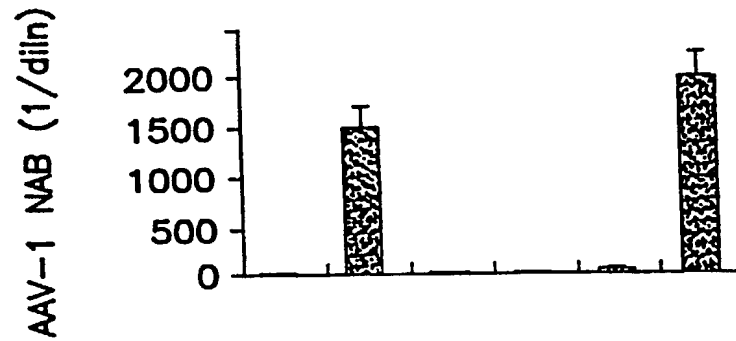
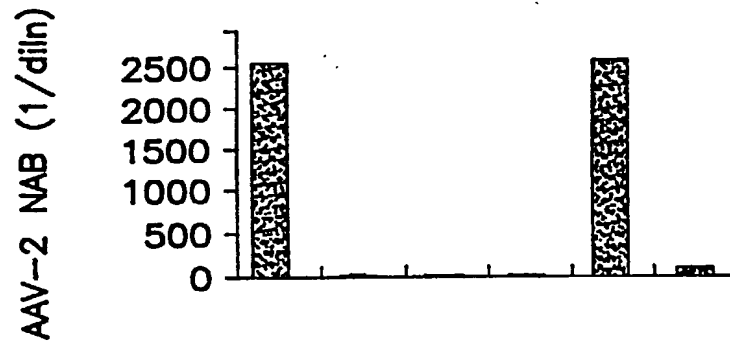


FIG. 5D



Group	1	2	3	4	5	6
Vector1- $\alpha 1AT$	AAV2	AAV1	PBS	PBS	AAV2	AAV1
Vector2-EPO	AAV2	AAV1	AAV2	AAV1	AAV1	AAV2

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FIG. 6A

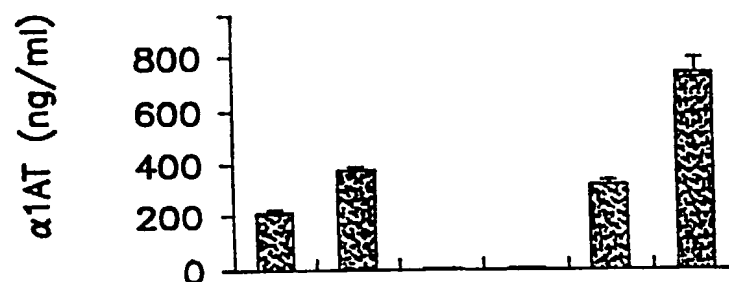


FIG. 6B

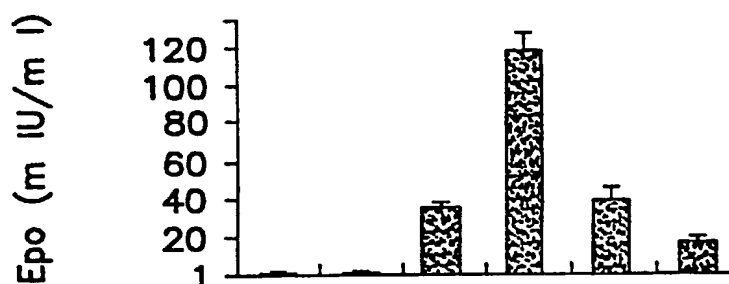


FIG. 6C

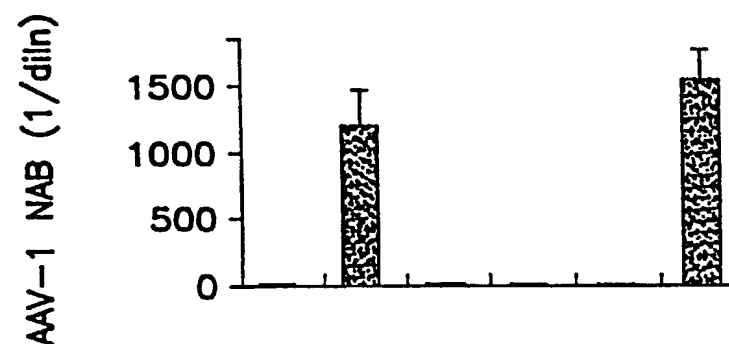
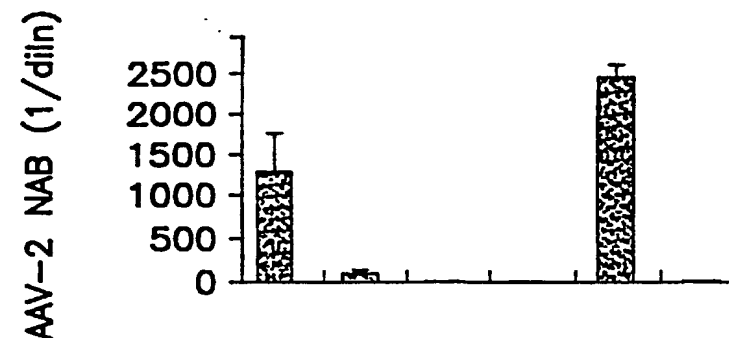


FIG. 6D

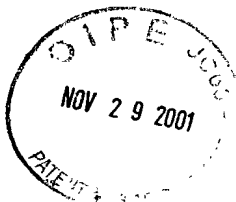


Group	1	2	3	4	5	6
Vector1- α 1AT	AAV2	AAV1	PBS	PBS	AAV2	AAV1
Vector2-EPO	AAV2	AAV1	AAV2	AAV1	AAV1	AAV2



00270

PATENT TRADEMARK OFFICE



DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled ADENO-ASSOCIATED VIRUS SEROTYPE I NUCLEIC ACID SEQUENCES, VECTORS AND HOST CELLS CONTAINING SAME, the specification of which

(check one) ☒ is attached hereto
☐ was filed on April 17, 2001 as Application No. 09/807,802 and was amended on April 17, 2001. (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed	Certified Copy Attached?	
(Number)	(Country)	(MM/DD/YYYY)		Yes	No

I hereby claim the benefit under 35 U.S.C. 119(e) of any United States provisional application(s) listed below.

60/107,114
(Application Number)

November 5, 1998
(Filing Date, MM/DD/YYYY)

I hereby appoint the following attorneys and agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

STANLEY B. KITA, Registration No. 24,561; GEORGE A. SMITH, JR., Registration No. 24,442; MARY E. BAK, Registration No. 31,215, CATHY A. KODROFF, Registration Number 33,980, WILLIAM BAK, Registration Number 37,277, HENRY HANSEN, Registration No. 19,612, and TRACY U. PALOVICH, Registration No. 47,840.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Inventor's signature _____

Date

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Citizenship: United States of America

Post Office Address: 1350 N. Avignon Drive, Gladwyne, Pennsylvania 19035

2-00
Full name of first inventor: Weidong Xiao

Inventor's signature _____

Weidong Xiao

11/27/01
Date

Residence: Fort Washington, Pennsylvania 19034

Citizenship: China CNX

Post Office Address: 1604 Conquest Way, Fort Washington, Pennsylvania 19034

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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WO 00/28061

PCT/US99/25694

SEQUENCE LISTING

<110> Wilson, James M.
Xiao, Weidong
The Trustees of the University of Pennsylvania

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Sequences, Vectors and Host Cells Containing Same

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PCT/US99/25694

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Glu Arg Lys Arg Leu Val Ala Gln His Leu Thr His Val Ser Gln Thr	
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PCT/US99/25694

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Ala Ser Tyr Ile Ser Phe Asn Ala Ala Ser Asn Ser Arg Ser Gln Ile	
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aag gcc gct ctg gac aat gcc ggc aag atc atg gcg ctg acc aaa tcc	1171
Lys Ala Ala Leu Asp Asn Ala Gly Lys Ile Met Ala Leu Thr Lys Ser	
265 270 275	
gcg ccc gac tac ctg gta ggc ccc gct ccg ccc gcg gac att aaa acc	1219
Ala Pro Asp Tyr Leu Val Gly Pro Ala Pro Pro Ala Asp Ile Lys Thr	
280 285 290 295	
aac cgc atc tac cgc atc ctg gag ctg aac ggc tac gaa cct gcc tac	1267
Asn Arg Ile Tyr Arg Ile Leu Glu Leu Asn Gly Tyr Glu Pro Ala Tyr	
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gcc ggc tcc gtc ttt ctc ggc tgg gcc cag aaa agg ttc ggg aag cgc	1315
Ala Gly Ser Val Phe Leu Gly Trp Ala Gln Lys Arg Phe Gly Lys Arg	
315 320 325	
aac acc atc tgg ctg ttt ggg ccg gcc acc acg ggc aag acc aac atc	1363
Asn Thr Ile Trp Leu Phe Gly Pro Ala Thr Thr Gly Lys Thr Asn Ile	
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gcg gaa gcc atc gcc cac gcc gtg ccc ttc tac ggc tgc gtc aac tgg	1411
Ala Glu Ala Ile Ala His Ala Val Pro Phe Tyr Gly Cys Val Asn Trp	
345 350 355	
acc aat gag aac ttt ccc ttc aat gat tgc gtc gac aag atg gtg atc	1459
Thr Asn Glu Asn Phe Pro Phe Asn Asp Cys Val Asp Lys Met Val Ile	
360 365 370 375	
tgg tgg gag gag ggc aag atg acg gcc aag gtc gtg gag tcc gcc aag	1507
Trp Trp Glu Glu Gly Lys Met Thr Ala Lys Val Val Glu Ser Ala Lys	
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gcc att ctc ggc ggc agc aag gtg cgc gtg gac caa aag tgc aag tcg 1555
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tcc gcc cag atc gac ccc acc ccc gtg atc gtc acc tcc aac acc aac 1603
Ser Ala Gln Ile Asp Pro Thr Pro Val Ile Val Thr Ser Asn Thr Asn 410 415 420

atg tgc gcc gtg att gac ggg aac agc acc acc ttc gag cac cag cag 1651
Met Cys Ala Val Ile Asp Gly Asn Ser Thr Thr Phe Glu His Gln Gln 425 430 435

ccg ttg cag gac cgg atg ttc aaa ttt gaa ctc acc cgc cgt ctg gag 1699
Pro Leu Gln Asp Arg Met Phe Lys Phe Glu Leu Thr Arg Arg Leu Glu 440 445 450 455

cat gac ttt ggc aag gtg aca aag cag gaa gtc aaa gag ttc ttc cgc 1747
His Asp Phe Gly Lys Val Thr Lys Gln Glu Val Lys Glu Phe Phe Arg 460 465 470

tgg gcg cag gat cac gtg acc gag gtg gcg cat gag ttc tac gtc aga 1795
Trp Ala Gln Asp His Val Thr Glu Val Ala His Glu Phe Tyr Val Arg 475 480 485

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Lys Gly Gly Ala Asn Lys Arg Pro Ala Pro Asp Asp Ala Asp Lys Ser 490 495 500

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Glu Pro Lys Arg Ala Cys Pro Ser Val Ala Asp Pro Ser Thr Ser Asp 505 510 515

gcg gaa gga gct ccg gtg gac ttt gcc gac agg tac caa aac aaa tgt 1939
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Ser Arg His Ala Gly Met Leu Gln Met Leu Phe Pro Cys Lys Thr Cys 540 545 550

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Arg Lys Arg Thr Tyr Arg Lys Leu Cys Ala Ile His His Leu Leu Gly	
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cgg gct ccc gag att gct tgc tcg gcc tgc gat ctg gtc aac gtg gac	2179
Arg Ala Pro Glu Ile Ala Cys Ser Ala Cys Asp Leu Val Asn Val Asp	
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Leu Asp Asp Cys Val Ser Glu Gln Met Ala Ala	
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gat ggt tat ctt cca gat tgg ctc gag gac aac ctc tct gag ggc att	2279
Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser Glu Gly Ile	
630 635 640	
cgc gag tgg tgg gac ttg aaa cct gga gcc ccg aag ccc aaa gcc aac	2327
Arg Glu Trp Trp Asp Leu Lys Pro Gly Ala Pro Lys Pro Lys Ala Asn	
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Gln Gln Lys Gln Asp Asp Gly Arg Gly Leu Val Leu Pro Gly Tyr Lys	
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tac ctc gga ccc ttc aac gga ctc gac aag ggg gag ccc gtc aac gcg	2423
Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro Val Asn Ala	
680 685 690	
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Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp Gln Gln Leu	
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Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala Asp Ala Glu	
710 715 720	
ttt cag gag cgt ctg caa gaa gat acg tct ttt ggg ggc aac ctc ggg	2567
Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly Asn Leu Gly	
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cga gca gtc ttc cag gcc aag aag cgg gtt ctc gaa cct ctc ggt ctg	2615
Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro Leu Gly Leu	
740 745 750 755	
gtt gag gaa ggc gct aag acg gct cct gga aag aaa cgt ccg gta gag	2663
Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg Pro Val Glu	
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cag tcg cca caa gag cca gac tcc tcc tcg ggc atc ggc aag aca ggc	2711
Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Ile Gly Lys Thr Gly	
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Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr Gly Asp Ser	
790 795 800	
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Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro Ala Thr Pro	
805 810 815	
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Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly Ala Pro Met	
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Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ala Ser Gly Asn	
840 845 850	
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Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val Ile Thr Thr Ser	
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Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu Tyr Lys Gln	
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Ile Ser Ser Ala Ser Thr Gly Ala Ser Asn Asp Asn His Tyr Phe Gly	
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Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe His Cys His	
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Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Asn Trp Gly Phe	
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cgg ccc aag aga ctc aac ttc aaa ctc ttc aac atc caa gtc aag gag	3191
Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln Val Lys Glu	
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Val Thr Thr Asn Asp Gly Val Thr Thr Ile Ala Asn Asn Leu Thr Ser	
950 955 960	

acg gtt caa gtc ttc tcg gac tcg gag tac cag ctt ccg tac gtc ctc 3287
 Thr Val Gln Val Phe Ser Asp Ser Glu Tyr Gln Leu Pro Tyr Val Leu
 965 970 975

ggc tct gcg cac cag ggc tgc ctc cct ccg ttc ccg gcg gac gtg ttc 3335
 Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala Asp Val Phe
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cct ttc cac agc agc tac gcg cac agc cag agc ctg gac cgg ctg atg 3527
 Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp Arg Leu Met
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aat cct ctc atc gac caa tac ctg tat tac ctg aac aga act caa aat 3575
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cag tcc gga agt gcc caa aac aag gac ttg ctg ttt agc cgt ggg tct 3623
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cca gct ggc atg tct gtt cag ccc aaa aac tgg cta cct gga ccc tgt 3671
 Pro Ala Gly Met Ser Val Gln Pro Lys Asn Trp Leu Pro Gly Pro Cys
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tat cgg cag cag cgc gtt tct aaa aca aaa aca gac aac aac aac agc 3719
 Tyr Arg Gln Gln Arg Val Ser Lys Thr Lys Thr Asp Asn Asn Asn Ser
 1110 1115 1120

aat ttt acc tgg act ggt gct tca aaa tat aac ctc aat ggg cgt gaa 3767
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tcc atc atc aac cct ggc act gct atg gcc tca cac aaa gac gac gaa 3815
 Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His Lys Asp Asp Glu
 1140 1145 1150 1155

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Asp Lys Phe Phe Pro Met Ser Gly Val Met Ile Phe Gly Lys Glu Ser	
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gcc gga gct tca aac act gca ttg gac aat gtc atg att aca gac gaa	3911
Ala Gly Ala Ser Asn Thr Ala Leu Asp Asn Val Met Ile Thr Asp Glu	
1175 1180 1185	
gag gaa att aaa gcc act aac cct gtg gcc acc gaa aga ttt ggg acc	3959
Glu Glu Ile Lys Ala Thr Asn Pro Val Ala Thr Glu Arg Phe Gly Thr	
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Val Ala Val Asn Phe Gln Ser Ser Ser Thr Asp Pro Ala Thr Gly Asp	
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Val His Ala Met Gly Ala Leu Pro Gly Met Val Trp Gln Asp Arg Asp	
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Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His Thr Asp Gly	
1240 1245 1250	
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His Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu Lys Asn Pro	
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Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala Asn Pro Pro	
1270 1275 1280	
gcg gag ttt tca gct aca aag ttt gct tca ttc atc acc caa tac tcc	4247
Ala Glu Phe Ser Ala Thr Lys Phe Ala Ser Phe Ile Thr Gln Tyr Ser	
1285 1290 1295	
aca gga caa gtg agt gtg gaa att gaa tgg gag ctg cag aaa gaa aac	4295
Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln Lys Glu Asn	
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Ser Lys Arg Trp Asn Pro Glu Val Gln Tyr Thr Ser Asn Tyr Ala Lys	
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tct gcc aac gtt gat ttt act gtg gac aac aat gga ctt tat act gag	4391
Ser Ala Asn Val Asp Phe Thr Val Asp Asn Asn Gly Leu Tyr Thr Glu	
1335 1340 1345	

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cct cgc ccc att ggc acc cgt tac ctt acc cgt ccc ctg taattacgtg 4440
Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Pro Leu
1350 1355 1360

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tatcggttac catggttata gcttacacat taactgcttg gttgcgcttc gcgataaaag 4560
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35 40 45
Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu
50 55 60
Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val
65 70 75 80
Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu
85 90 95
Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile
100 105 110
Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu
115 120 125
Pro Asn Trp Phe Ala Val Thr Lys Thr Arg Asn Gly Ala Gly Gly Gly
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Asn	Lys	Val	Val	Asp	Glu	Cys	Tyr	Ile	Pro	Asn	Tyr	Leu	Leu	Pro	Lys	145	150	155	160
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Ser	Ala	Cys	Leu	Asn	Leu	Ala	Glu	Arg	Lys	Arg	Leu	Val	Ala	Gln	His	180	185	190	
Leu	Thr	His	Val	Ser	Gln	Thr	Gln	Glu	Gln	Asn	Lys	Glu	Asn	Leu	Asn	195	200	205	
Pro	Asn	Ser	Asp	Ala	Pro	Val	Ile	Arg	Ser	Lys	Thr	Ser	Ala	Arg	Tyr	210	215	220	
Met	Glu	Leu	Val	Gly	Trp	Leu	Val	Asp	Arg	Gly	Ile	Thr	Ser	Glu	Lys	225	230	235	240
Gln	Trp	Ile	Gln	Glu	Asp	Gln	Ala	Ser	Tyr	Ile	Ser	Phe	Asn	Ala	Ala	245	250	255	
Ser	Asn	Ser	Arg	Ser	Gln	Ile	Lys	Ala	Ala	Leu	Asp	Asn	Ala	Gly	Lys	260	265	270	
Ile	Met	Ala	Leu	Thr	Lys	Ser	Ala	Pro	Asp	Tyr	Leu	Val	Gly	Pro	Ala	275	280	285	
Pro	Pro	Ala	Asp	Ile	Lys	Thr	Asn	Arg	Ile	Tyr	Arg	Ile	Leu	Glu	Leu	290	295	300	
Asn	Gly	Tyr	Glu	Pro	Ala	Tyr	Ala	Gly	Ser	Val	Phe	Leu	Gly	Trp	Ala	305	310	315	320
Gln	Lys	Arg	Phe	Gly	Lys	Arg	Asn	Thr	Ile	Trp	Leu	Phe	Gly	Pro	Ala	325	330	335	
Thr	Thr	Gly	Lys	Thr	Asn	Ile	Ala	Glu	Ala	Ile	Ala	His	Ala	Val	Pro	340	345	350	
Phe	Tyr	Gly	Cys	Val	Asn	Trp	Thr	Asn	Glu	Asn	Phe	Pro	Phe	Asn	Asp	355	360	365	
Cys	Val	Asp	Lys	Met	Val	Ile	Trp	Trp	Glu	Glu	Gly	Lys	Met	Thr	Ala	370	375	380	
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Lys Ala Asn Gln Gln Lys Gln Asp Asp Gly Arg Gly Leu Val Leu Pro
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Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro
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Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
 65           70           75           80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala
          85           90           95

Asp Ala Glu Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly
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Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro
          115          120          125

Leu Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg
          130          135          140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Ile Gly
          145          150          155          160

Lys Thr Gly Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
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Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro
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Ala Thr Pro Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly
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Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ala
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Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val Ile
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Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu

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Lys	Glu	Ser	Ala	Gly	Ala	Ser	Asn	Thr	Ala	Leu	Asp	Asn	Val	Met	Ile
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Thr	Gly	Asp	Val	His	Ala	Met	Gly	Ala	Leu	Pro	Gly	Met	Val	Trp	Gln
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610				615				620							
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Lys	Asn	Pro	Pro	Pro	Gln	Ile	Leu	Ile	Lys	Asn	Thr	Pro	Val	Pro	Ala
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660				665				670							
Gln	Tyr	Ser	Thr	Gly	Gln	Val	Ser	Val	Glu	Ile	Glu	Trp	Glu	Leu	Gln
675				680				685							
Lys	Glu	Asn	Ser	Lys	Arg	Trp	Asn	Pro	Glu	Val	Gln	Tyr	Thr	Ser	Asn
690				695				700							
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705				710				715				720			
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gag cac ctg ccg ggc att tct gac tcg ttt gtg agc tgg gtg gcc gag      96
Glu His Leu Pro Gly Ile Ser Asp Ser Phe Val Ser Trp Val Ala Glu
           20             25             30

aag gaa tgg gag ctg ccc ccg gat tct gac atg gat ctg aat ctg att     144
Lys Glu Trp Glu Leu Pro Pro Asp Ser Asp Met Asp Leu Asn Leu Ile
           35             40             45

gag cag gca ccc ctg acc gtg gcc gag aag ctg cag cgc gac ttc ctg     192
Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu
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Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val
           65             70             75             80

cag ttc gag aag ggc gag tcc tac ttc cac ctc cat att ctg gtg gag     288
Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu
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acc acg ggg gtc aaa tcc atg gtg ctg ggc cgc ttc ctg agt cag att     336
Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile
           100            105            110

agg gac aag ctg gtg cag acc atc tac cgc ggg atc gag ccg acc ctg     384
Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu
           115            120            125

ccc aac tgg ttc gcg gtg acc aag acg cgt aat ggc gcc gga ggg ggg     432
Pro Asn Trp Phe Ala Val Thr Lys Thr Arg Asn Gly Ala Gly Gly Gly
           130            135            140

aac aag gtg gtg gac gag tgc tac atc ccc aac tac ctc ctg ccc aag     480
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           145            150            155            160

act cag ccc gag ctg cag tgg gcg tgg act aac atg gag gag tat ata     528

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180 185 190	
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Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Leu Asn	
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ccc aat tct gac gcg cct gtc atc cgg tca aaa acc tcc gcg cgc tac	672
Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr	
210 215 220	
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Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys	
225 230 235 240	
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Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala	
245 250 255	
tcc aac tcg cgg tcc cag atc aag gcc gct ctg gac aat gcc ggc aag	816
Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys	
260 265 270	
atc atg gcg ctg acc aaa tcc gcg ccc gac tac ctg gta ggc ccc gct	864
Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala	
275 280 285	
ccg ccc gcg gac att aaa acc aac cgc atc tac cgc atc ctg gag ctg	912
Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu	
290 295 300	
aac ggc tac gaa cct gcc tac gcc ggc tcc gtc ttt ctc ggc tgg gcc	960
Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala	
305 310 315 320	
cag aaa agg ttc ggg aag cgc aac acc atc tgg ctg ttt ggg ccg gcc	1008
Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala	
325 330 335	
acc acg ggc aag acc aac atc gcg gaa gcc atc gcc cac gcc gtg ccc	1056
Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro	
340 345 350	
ttc tac ggc tgc gtc aac tgg acc aat gag aac ttt ccc ttc aat gat	1104

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Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp	
355 360 365	
tgc gtc gac aag atg gtg atc tgg tgg gag gag ggc aag atg acg gcc	1152
Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala	
370 375 380	
aag gtc gtg gag tcc gcc aag gcc att ctc ggc ggc agc aag gtg cgc	1200
Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg	
385 390 395 400	
gtg gac caa aag tgc aag tcg tcc gcc cag atc gac ccc acc ccc gtg	1248
Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val	
405 410 415	
atc gtc acc tcc aac acc aac atg tgc gcc gtg att gac ggg aac agc	1296
Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser	
420 425 430	
acc acc ttc gag cac cag cag ccg ttg cag gac cgg atg ttc aaa ttt	1344
Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe	
435 440 445	
gaa ctc acc cgc cgt ctg gag cat gac ttt ggc aag gtg aca aag cag	1392
Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln	
450 455 460	
gaa gtc aaa gag ttc ttc cgc tgg gcg cag gat cac gtg acc gag gtg	1440
Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val	
465 470 475 480	
gcg cat gag ttc tac gtc aga aag ggt gga gcc aac aaa aga ccc gcc	1488
Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala	
485 490 495	
ccc gat gac gcg gat aaa agc gag ccc aag cgg gcc tgc ccc tca gtc	1536
Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val	
500 505 510	
gcg gat cca tcg acg tca gac gcg gaa gga gct ccg gtg gac ttt gcc	1584
Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala	
515 520 525	
gac agg tac caa aac aaa tgt tct cgt cac gcg ggc atg ctt cag atg	1632
Asp Arg Tyr Gln Asn Lys Cys Ser Arg His Ala Gly Met Leu Gln Met	
530 535 540	
ctg ttt ccc tgc aag aca tgc gag aga atg aat cag aat ttc aac att	1680

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Leu Phe Pro Cys Lys Thr Cys Glu Arg Met Asn Gln Asn Phe Asn Ile
 545 550 555 560

tgc ttc acg cac ggg acg aga gac tgt tca gag tgc ttc ccc ggc gtg 1728
 Cys Phe Thr His Gly Thr Arg Asp Cys Ser Glu Cys Phe Pro Gly Val
 565 570 575

tca gaa tct caa ccg gtc gtc aga aag agg acg tat cgg aaa ctc tgt 1776
 Ser Glu Ser Gln Pro Val Val Arg Lys Arg Thr Tyr Arg Lys Leu Cys
 580 585 590

gcc att cat cat ctg ctg ggg cgg gct ccc gag att gct tgc tcg gcc 1824
 Ala Ile His His Leu Leu Gly Arg Ala Pro Glu Ile Ala Cys Ser Ala
 595 600 605

tgc gat ctg gtc aac gtg gac ctg gat gac tgt gtt tct gag caa taa 1872
 Cys Asp Leu Val Asn Val Asp Leu Asp Asp Cys Val Ser Glu Gln
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Glu His Leu Pro Gly Ile Ser Asp Ser Phe Val Ser Trp Val Ala Glu
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Lys Glu Trp Glu Leu Pro Pro Asp Ser Asp Met Asp Leu Asn Leu Ile
 35 40 45

Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu
 50 55 60

Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val
 65 70 75 80

Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu
 85 90 95

Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile
 100 105 110

Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu

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<210> 6

<211> 1641

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<213> AAV-1

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gag cac ctg ccg ggc att tct gac tcg ttt gtg agc tgg gtg gcc gag      96
Glu His Leu Pro Gly Ile Ser Asp Ser Phe Val Ser Trp Val Ala Glu
           20             25             30

aag gaa tgg gag ctg ccc ccg gat tct gac atg gat ctg aat ctg att     144
Lys Glu Trp Glu Leu Pro Pro Asp Ser Asp Met Asp Leu Asn Leu Ile
           35             40             45

gag cag gca ccc ctg acc gtg gcc gag aag ctg cag cgc gac ttc ctg     192
Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu
           50             55             60

gtc caa tgg cgc cgc gtg agt aag gcc ccg gag gcc ctc ttc ttt gtt     240
Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val
           65             70             75             80

cag ttc gag aag ggc gag tcc tac ttc cac ctc cat att ctg gtg gag     288
Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu
           85             90             95

acc acg ggg gtc aaa tcc atg gtg ctg ggc cgc ttc ctg agt cag att     336
Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile
           100            105            110

agg gac aag ctg gtg cag acc atc tac cgc ggg atc gag ccg acc ctg     384
Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu
           115            120            125

ccc aac tgg ttc gcg gtg acc aag acg cgt aat ggc gcc gga ggg ggg     432
Pro Asn Trp Phe Ala Val Thr Lys Thr Arg Asn Gly Ala Gly Gly Gly
           130            135            140

aac aag gtg gtg gac gag tgc tac atc ccc aac tac ctc ctg ccc aag     480
Asn Lys Val Val Asp Glu Cys Tyr Ile Pro Asn Tyr Leu Leu Pro Lys

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145	150	155	160	
act cag ccc gag ctg cag tgg gcg tgg act aac atg gag gag tat ata				528
Thr Gln Pro Glu Leu Gln Trp Ala Trp Thr Asn Met Glu Glu Tyr Ile				
	165	170	175	
agc gcc tgt ttg aac ctg gcc gag cgc aaa cgg ctc gtg gcg cag cac				576
Ser Ala Cys Leu Asn Leu Ala Glu Arg Lys Arg Leu Val Ala Gln His				
	180	185	190	
ctg acc cac gtc agc cag acc cag gag cag aac aag gag aat ctg aac				624
Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Leu Asn				
	195	200	205	
ccc aat tct gac gcg cct gtc atc cgg tca aaa acc tcc gcg cgc tac				672
Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr				
	210	215	220	
atg gag ctg gtc ggg tgg ctg gtg gac cgg ggc atc acc tcc gag aag				720
Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys				
	225	230	235	240
cag tgg atc cag gag gac cag gcc tcg tac atc tcc ttc aac gcc gct				768
Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala				
	245	250	255	
tcc aac tcg cgg tcc cag atc aag gcc gct ctg gac aat gcc ggc aag				816
Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys				
	260	265	270	
atc atg gcg ctg acc aaa tcc gcg ccc gac tac ctg gta ggc ccc gct				864
Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala				
	275	280	285	
ccg ccc gcg gac att aaa acc aac cgc atc tac cgc atc ctg gag ctg				912
Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu				
	290	295	300	
aac ggc tac gaa cct gcc tac gcc ggc tcc gtc ttt ctc ggc tgg gcc				960
Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala				
	305	310	315	320
cag aaa agg ttc ggg aag cgc aac acc atc tgg ctg ttt ggg ccg gcc				1008
Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala				
	325	330	335	
acc acg ggc aag acc aac atc gcg gaa gcc atc gcc cac gcc gtg ccc				1056
Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro				

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340	345	350	
ttc tac ggc tgc gtc aac tgg acc aat gag aac ttt ccc ttc aat gat			1104
Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp			
355	360	365	
tgc gtc gac aag atg gtg atc tgg tgg gag gag ggc aag atg acg gcc			1152
Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala			
370	375	380	
aag gtc gtg gag tcc gcc aag gcc att ctc ggc ggc agc aag gtg cgc			1200
Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg			
385	390	395	400
gtg gac caa aag tgc aag tcg tcc gcc cag atc gac ccc acc ccc gtg			1248
Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val			
405	410	415	
atc gtc acc tcc aac acc aac atg tgc gcc gtg att gac ggg aac agc			1296
Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser			
420	425	430	
acc acc ttc gag cac cag cag ccg ttg cag gac cgg atg ttc aaa ttt			1344
Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe			
435	440	445	
gaa ctc acc cgc cgt ctg gag cat gac ttt ggc aag gtg aca aag cag			1392
Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln			
450	455	460	
gaa gtc aaa gag ttc ttc cgc tgg gcg cag gat cac gtg acc gag gtg			1440
Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val			
465	470	475	480
gcg cat gag ttc tac gtc aga aag ggt gga gcc aac aaa aga ccc gcc			1488
Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala			
485	490	495	
ccc gat gac gcg gat aaa agc gag ccc aag cgg gcc tgc ccc tca gtc			1536
Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val			
500	505	510	
gcg gat cca tcg acg tca gac gcg gaa gga gct ccg gtg gac ttt gcc			1584
Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala			
515	520	525	
gac agg tat ggc tgc cga tgg tta tct tcc aga ttg gct cga gga caa			1632
Asp Arg Tyr Gly Cys Arg Trp Leu Ser Ser Arg Leu Ala Arg Gly Gln			

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PCT/US99/25694

530 535 540

cct ctc tga 1641

Pro Leu

545

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20 25 30

Lys Glu Trp Glu Leu Pro Pro Asp Ser Asp Met Asp Leu Asn Leu Ile

35 40 45

Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu

50 55 60

Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val

65 70 75 80

Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu

85 90 95

Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile

100 105 110

Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu

115 120 125

Pro Asn Trp Phe Ala Val Thr Lys Thr Arg Asn Gly Ala Gly Gly Gly

130 135 140

Asn Lys Val Val Asp Glu Cys Tyr Ile Pro Asn Tyr Leu Leu Pro Lys

145 150 155 160

Thr Gln Pro Glu Leu Gln Trp Ala Trp Thr Asn Met Glu Glu Tyr Ile

165 170 175

Ser Ala Cys Leu Asn Leu Ala Glu Arg Lys Arg Leu Val Ala Gln His

180 185 190

Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Leu Asn
 195 200 205
 Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr
 210 215 220
 Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys
 225 230 235 240
 Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
 245 250 255
 Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
 260 265 270
 Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
 275 280 285
 Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu
 290 295 300
 Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala
 305 310 315 320
 Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala
 325 330 335
 Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro
 340 345 350
 Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp
 355 360 365
 Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala
 370 375 380
 Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg
 385 390 395 400
 Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val
 405 410 415
 Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser
 420 425 430
 Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe
 435 440 445

WO 00/28061

PCT/US99/25694

Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln
450 455 460

Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val
465 470 475 480

Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala
485 490 495

Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val
500 505 510

Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
515 520 525

Asp Arg Tyr Gly Cys Arg Trp Leu Ser Ser Arg Leu Ala Arg Gly Gln
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Pro Leu
545

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cag tgg atc cag gag gac cag gcc tcg tac atc tcc ttc aac gcc gct 96
Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
20 25 30

tcc aac tcg cgg tcc cag atc aag gcc gct ctg gac aat gcc ggc aag 144
Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
35 40 45

atc atg gcg ctg acc aaa tcc gcg ccc gac tac ctg gta ggc ccc gct 192
Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
50 55 60

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ccg ccc gcg gac att aaa acc aac cgc atc tac cgc atc ctg gag ctg      240
Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu
  65                      70                      75                      80

aac ggc tac gaa cct gcc tac gcc ggc tcc gtc ttt ctc ggc tgg gcc      288
Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala
      85                      90                      95

cag aaa agg ttc ggg aag cgc aac acc atc tgg ctg ttt ggg ccg gcc      336
Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala
      100                      105                      110

acc acg ggc aag acc aac atc gcg gaa gcc atc gcc cac gcc gtg ccc      384
Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro
      115                      120                      125

ttc tac ggc tgc gtc aac tgg acc aat gag aac ttt ccc ttc aat gat      432
Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp
      130                      135                      140

tgc gtc gac aag atg gtg atc tgg tgg gag gag ggc aag atg acg gcc      480
Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala
      145                      150                      155                      160

aag gtc gtg gag tcc gcc aag gcc att ctc ggc ggc agc aag gtg cgc      528
Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg
      165                      170                      175

gtg gac caa aag tgc aag tgc tcc gcc cag atc gac ccc acc ccc gtg      576
Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val
      180                      185                      190

atc gtc acc tcc aac acc aac atg tgc gcc gtg att gac ggg aac agc      624
Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser
      195                      200                      205

acc acc ttc gag cac cag cag ccg ttg cag gac cgg atg ttc aaa ttt      672
Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe
      210                      215                      220

gaa ctc acc cgc cgt ctg gag cat gac ttt ggc aag gtg aca aag cag      720
Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln
      225                      230                      235                      240

gaa gtc aaa gag ttc ttc cgc tgg gcg cag gat cac gtg acc gag gtg      768
Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val
      245                      250                      255

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PCT/US99/25694

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260 265 270

ccc gat gac gcg gat aaa agc gag ccc aag cgg gcc tgc ccc tca gtc 864
Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val
275 280 285

gcg gat cca tcg acg tca gac gcg gaa gga gct ccg gtg gac ttt gcc 912
Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
290 295 300

gac agg tac caa aac aaa tgt tct cgt cac gcg ggc atg ctt cag atg 960
Asp Arg Tyr Gln Asn Lys Cys Ser Arg His Ala Gly Met Leu Gln Met
305 310 315 320

ctg ttt ccc tgc aag aca tgc gag aga atg aat cag aat ttc aac att 1008
Leu Phe Pro Cys Lys Thr Cys Glu Arg Met Asn Gln Asn Phe Asn Ile
325 330 335

tgc ttc acg cac ggg acg aga gac tgt tca gag tgc ttc ccc ggc gtg 1056
Cys Phe Thr His Gly Thr Arg Asp Cys Ser Glu Cys Phe Pro Gly Val
340 345 350

tca gaa tct caa ccg gtc gtc aga aag agg acg tat cgg aaa ctc tgt 1104
Ser Glu Ser Gln Pro Val Val Arg Lys Arg Thr Tyr Arg Lys Leu Cys
355 360 365

gcc att cat cat ctg ctg ggg cgg gct ccc gag att gct tgc tcg gcc 1152
Ala Ile His His Leu Leu Gly Arg Ala Pro Glu Ile Ala Cys Ser Ala
370 375 380

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Cys Asp Leu Val Asn Val Asp Leu Asp Asp Cys Val Ser Glu Gln
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Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys	35	40	45			
Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala	50	55	60			
Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu	65	70	75	80		
Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala	85	90	95			
Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala	100	105	110			
Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro	115	120	125			
Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp	130	135	140			
Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala	145	150	155	160		
Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg	165	170	175			
Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val	180	185	190			
Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser	195	200	205			
Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe	210	215	220			
Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln	225	230	235	240		
Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val	245	250	255			
Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala	260	265	270			
Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val						

275 280 285
 Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
 290 295 300
 Asp Arg Tyr Gln Asn Lys Cys Ser Arg His Ala Gly Met Leu Gln Met
 305 310 315 320
 Leu Phe Pro Cys Lys Thr Cys Glu Arg Met Asn Gln Asn Phe Asn Ile
 325 330 335
 Cys Phe Thr His Gly Thr Arg Asp Cys Ser Glu Cys Phe Pro Gly Val
 340 345 350
 Ser Glu Ser Gln Pro Val Val Arg Lys Arg Thr Tyr Arg Lys Leu Cys
 355 360 365
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 cag tgg atc cag gag gac cag gcc tcg tac atc tcc ttc aac gcc gct 96
 Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
 20 25 30
 tcc aac tcg cgg tcc cag atc aag gcc gct ctg gac aat gcc ggc aag 144

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Ser	Asn	Ser	Arg	Ser	Gln	Ile	Lys	Ala	Ala	Leu	Asp	Asn	Ala	Gly	Lys	
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atc	atg	gcg	ctg	acc	aaa	tcc	gcg	ccc	gac	tac	ctg	gta	ggc	ccc	gct	192
Ile	Met	Ala	Leu	Thr	Lys	Ser	Ala	Pro	Asp	Tyr	Leu	Val	Gly	Pro	Ala	
	50					55					60					
ccg	ccc	gcg	gac	att	aaa	acc	aac	cgc	atc	tac	cgc	atc	ctg	gag	ctg	240
Pro	Pro	Ala	Asp	Ile	Lys	Thr	Asn	Arg	Ile	Tyr	Arg	Ile	Leu	Glu	Leu	
	65				70				75					80		
aac	ggc	tac	gaa	cct	gcc	tac	gcc	ggc	tcc	gtc	ttt	ctc	ggc	tgg	gcc	288
Asn	Gly	Tyr	Glu	Pro	Ala	Tyr	Ala	Gly	Ser	Val	Phe	Leu	Gly	Trp	Ala	
				85				90						95		
cag	aaa	agg	ttc	ggg	aag	cgc	aac	acc	atc	tgg	ctg	ttt	ggg	ccg	gcc	336
Gln	Lys	Arg	Phe	Gly	Lys	Arg	Asn	Thr	Ile	Trp	Leu	Phe	Gly	Pro	Ala	
			100					105					110			
acc	acg	ggc	aag	acc	aac	atc	gcg	gaa	gcc	atc	gcc	cac	gcc	gtg	ccc	384
Thr	Thr	Gly	Lys	Thr	Asn	Ile	Ala	Glu	Ala	Ile	Ala	His	Ala	Val	Pro	
		115					120					125				
ttc	tac	ggc	tgc	gtc	aac	tgg	acc	aat	gag	aac	ttt	ccc	ttc	aat	gat	432
Phe	Tyr	Gly	Cys	Val	Asn	Trp	Thr	Asn	Glu	Asn	Phe	Pro	Phe	Asn	Asp	
		130				135					140					
tgc	gtc	gac	aag	atg	gtg	atc	tgg	tgg	gag	gag	ggc	aag	atg	acg	gcc	480
Cys	Val	Asp	Lys	Met	Val	Ile	Trp	Trp	Glu	Glu	Gly	Lys	Met	Thr	Ala	
	145				150				155					160		
aag	gtc	gtg	gag	tcc	gcc	aag	gcc	att	ctc	ggc	ggc	agc	aag	gtg	cgc	528
Lys	Val	Val	Glu	Ser	Ala	Lys	Ala	Ile	Leu	Gly	Gly	Ser	Lys	Val	Arg	
				165				170						175		
gtg	gac	caa	aag	tgc	aag	tcg	tcc	gcc	cag	atc	gac	ccc	acc	ccc	gtg	576
Val	Asp	Gln	Lys	Cys	Lys	Ser	Ser	Ala	Gln	Ile	Asp	Pro	Thr	Pro	Val	
			180					185						190		
atc	gtc	acc	tcc	aac	acc	aac	atg	tgc	gcc	gtg	att	gac	ggg	aac	agc	624
Ile	Val	Thr	Ser	Asn	Thr	Asn	Met	Cys	Ala	Val	Ile	Asp	Gly	Asn	Ser	
		195					200					205				
acc	acc	ttc	gag	cac	cag	cag	ccg	ttg	cag	gac	cgg	atg	ttc	aaa	ttt	672
Thr	Thr	Phe	Glu	His	Gln	Gln	Pro	Leu	Gln	Asp	Arg	Met	Phe	Lys	Phe	
		210				215					220					
gaa	ctc	acc	cgc	cgt	ctg	gag	cat	gac	ttt	ggc	aag	gtg	aca	aag	cag	720

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Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln
 225 230 235 240

gaa gtc aaa gag ttc ttc cgc tgg gcg cag gat cac gtg acc gag gtg 768
 Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val
 245 250 255

gcg cat gag ttc tac gtc aga aag ggt gga gcc aac aaa aga ccc gcc 816
 Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala
 260 265 270

ccc gat gac gcg gat aaa agc gag ccc aag cgg gcc tgc ccc tca gtc 864
 Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val
 275 280 285

gcg gat cca tcg acg tca gac gcg gaa gga gct ccg gtg gac ttt gcc 912
 Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
 290 295 300

gac agg tat ggc tgc cga tgg tta tct tcc aga ttg gct cga gga caa 960
 Asp Arg Tyr Gly Cys Arg Trp Leu Ser Ser Arg Leu Ala Arg Gly Gln
 305 310 315 320

cct ctc tga 969
 Pro Leu

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 <212> PRT
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Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
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Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
 35 40 45

Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
 50 55 60

Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu
 65 70 75 80

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Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala
85 90 95

Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala
100 105 110

Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro
115 120 125

Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp
130 135 140

Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala
145 150 155 160

Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg
165 170 175

Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val
180 185 190

Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser
195 200 205

Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe
210 215 220

Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln
225 230 235 240

Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val
245 250 255

Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala
260 265 270

Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val
275 280 285

Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
290 295 300

Asp Arg Tyr Gly Cys Arg Trp Leu Ser Ser Arg Leu Ala Arg Gly Gln
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Pro Leu

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gag ggc att cgc gag tgg tgg gac ttg aaa cct gga gcc ccg aag ccc	96
Glu Gly Ile Arg Glu Trp Trp Asp Leu Lys Pro Gly Ala Pro Lys Pro	
20 25 30	

aaa gcc aac cag caa aag cag gac gac ggc cgg ggt ctg gtg ctt cct	144
Lys Ala Asn Gln Gln Lys Gln Asp Asp Gly Arg Gly Leu Val Leu Pro	
35 40 45	

ggc tac aag tac ctc gga ccc ttc aac gga ctc gac aag ggg gag ccc	192
Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro	
50 55 60	

gtc aac gcg gcg gac gca gcg gcc ctc gag cac gac aag gcc tac gac	240
Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp	
65 70 75 80	

cag cag ctc aaa gcg ggt gac aat ccg tac ctg cgg tat aac cac gcc	288
Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala	
85 90 95	

gac gcc gag ttt cag gag cgt ctg caa gaa gat acg tct ttt ggg ggc	336
Asp Ala Glu Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly	
100 105 110	

aac ctc ggg cga gca gtc ttc cag gcc aag aag cgg gtt ctc gaa cct	384
Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro	
115 120 125	

ctc ggt ctg gtt gag gaa ggc gct aag acg gct cct gga aag aaa cgt	432
Leu Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg	
130 135 140	

ccg gta gag cag tcg cca caa gag cca gac tcc tcc tcg ggc atc ggc	480
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Pro Val Glu Gln Ser	Pro Gln Glu Pro Asp Ser Ser Ser Gly Ile Gly	
145	150	155 160
aag aca ggc cag cag ccc gct aaa aag aga ctc aat ttt ggt cag act		528
Lys Thr Gly Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr		
	165 170	175
ggc gac tca gag tca gtc ccc gat cca caa cct ctc gga gaa cct cca		576
Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro		
	180 185	190
gca acc ccc gct gct gtg gga cct act aca atg gct tca ggc ggt ggc		624
Ala Thr Pro Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly		
	195 200	205
gca cca atg gca gac aat aac gaa ggc gcc gac gga gtg ggt aat gcc		672
Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ala		
	210 215	220
tca gga aat tgg cat tgc gat tcc aca tgg ctg ggc gac aga gtc atc		720
Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val Ile		
	225 230	235 240
acc acc agc acc cgc acc tgg gcc ttg ccc acc tac aat aac cac ctc		768
Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu		
	245 250	255
tac aag caa atc tcc agt gct tca acg ggg gcc agc aac gac aac cac		816
Tyr Lys Gln Ile Ser Ser Ala Ser Thr Gly Ala Ser Asn Asp Asn His		
	260 265	270
tac ttc ggc tac agc acc ccc tgg ggg tat ttt gat ttc aac aga ttc		864
Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe		
	275 280	285
cac tgc cac ttt tca cca cgt gac tgg cag cga ctc atc aac aac aat		912
His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Asn		
	290 295	300
tgg gga ttc cgg ccc aag aga ctc aac ttc aaa ctc ttc aac atc caa		960
Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln		
	305 310	315 320
gtc aag gag gtc acg acg aat gat ggc gtc aca acc atc gct aat aac		1008
Val Lys Glu Val Thr Thr Asn Asp Gly Val Thr Thr Ile Ala Asn Asn		
	325 330	335
ctt acc agc acg gtt caa gtc ttc tcg gac tcg gag tac cag ctt ccg		1056

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Leu Thr Ser Thr Val Gln Val Phe Ser Asp Ser Glu Tyr Gln Leu Pro	
340 345 350	
tac gtc ctc ggc tct gcg cac cag ggc tgc ctc cct ccg ttc ccg gcg	1104
Tyr Val Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala	
355 360 365	
gac gtg ttc atg att ccg caa tac ggc tac ctg acg ctc aac aat ggc	1152
Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly	
370 375 380	
agc caa gcc gtg gga cgt tca tcc ttt tac tgc ctg gaa tat ttc cct	1200
Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe Pro	
385 390 395 400	
tct cag atg ctg aga acg ggc aac aac ttt acc ttc agc tac acc ttt	1248
Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Thr Phe Ser Tyr Thr Phe	
405 410 415	
gag gaa gtg cct ttc cac agc agc tac gcg cac agc cag agc ctg gac	1296
Glu Glu Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp	
420 425 430	
cgg ctg atg aat cct ctc atc gac caa tac ctg tat tac ctg aac aga	1344
Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Asn Arg	
435 440 445	
act caa aat cag tcc gga agt gcc caa aac aag gac ttg ctg ttt agc	1392
Thr Gln Asn Gln Ser Gly Ser Ala Gln Asn Lys Asp Leu Leu Phe Ser	
450 455 460	
cgt ggg tct cca gct ggc atg tct gtt cag ccc aaa aac tgg cta cct	1440
Arg Gly Ser Pro Ala Gly Met Ser Val Gln Pro Lys Asn Trp Leu Pro	
465 470 475 480	
gga ccc tgt tat cgg cag cag cgc gtt tct aaa aca aaa aca gac aac	1488
Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Lys Thr Lys Thr Asp Asn	
485 490 495	
aac aac agc aat ttt acc tgg act ggt gct tca aaa tat aac ctc aat	1536
Asn Asn Ser Asn Phe Thr Trp Thr Gly Ala Ser Lys Tyr Asn Leu Asn	
500 505 510	
ggg cgt gaa tcc atc atc aac cct ggc act gct atg gcc tca cac aaa	1584
Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His Lys	
515 520 525	
gac gac gaa gac aag ttc ttt ccc atg agc ggt gtc atg att ttt gga	1632

37

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PCT/US99/25694

Tyr Thr Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Pro Leu
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taa 2211

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20 25 30

Lys Ala Asn Gln Gln Lys Gln Asp Asp Gly Arg Gly Leu Val Leu Pro
35 40 45

Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro
50 55 60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65 70 75 80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala
85 90 95

Asp Ala Glu Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly
100 105 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro
115 120 125

Leu Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg
130 135 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Ile Gly
145 150 155 160

Lys Thr Gly Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
165 170 175

Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro
180 185 190

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Ala Thr Pro Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly
195 200 205

Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ala
210 215 220

Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val Ile
225 230 235 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
245 250 255

Tyr Lys Gln Ile Ser Ser Ala Ser Thr Gly Ala Ser Asn Asp Asn His
260 265 270

Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe
275 280 285

His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Asn
290 295 300

Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln
305 310 315 320

Val Lys Glu Val Thr Thr Asn Asp Gly Val Thr Thr Ile Ala Asn Asn
325 330 335

Leu Thr Ser Thr Val Gln Val Phe Ser Asp Ser Glu Tyr Gln Leu Pro
340 345 350

Tyr Val Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala
355 360 365

Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly
370 375 380

Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe Pro
385 390 395 400

Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Thr Phe Ser Tyr Thr Phe
405 410 415

Glu Glu Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp
420 425 430

Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Asn Arg
435 440 445

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Thr	Gln	Asn	Gln	Ser	Gly	Ser	Ala	Gln	Asn	Lys	Asp	Leu	Leu	Phe	Ser	450	455	460	
Arg	Gly	Ser	Pro	Ala	Gly	Met	Ser	Val	Gln	Pro	Lys	Asn	Trp	Leu	Pro	465	470	475	480
Gly	Pro	Cys	Tyr	Arg	Gln	Gln	Arg	Val	Ser	Lys	Thr	Lys	Thr	Asp	Asn	485	490	495	
Asn	Asn	Ser	Asn	Phe	Thr	Trp	Thr	Gly	Ala	Ser	Lys	Tyr	Asn	Leu	Asn	500	505	510	
Gly	Arg	Glu	Ser	Ile	Ile	Asn	Pro	Gly	Thr	Ala	Met	Ala	Ser	His	Lys	515	520	525	
Asp	Asp	Glu	Asp	Lys	Phe	Phe	Pro	Met	Ser	Gly	Val	Met	Ile	Phe	Gly	530	535	540	
Lys	Glu	Ser	Ala	Gly	Ala	Ser	Asn	Thr	Ala	Leu	Asp	Asn	Val	Met	Ile	545	550	555	560
Thr	Asp	Glu	Glu	Glu	Ile	Lys	Ala	Thr	Asn	Pro	Val	Ala	Thr	Glu	Arg	565	570	575	
Phe	Gly	Thr	Val	Ala	Val	Asn	Phe	Gln	Ser	Ser	Ser	Thr	Asp	Pro	Ala	580	585	590	
Thr	Gly	Asp	Val	His	Ala	Met	Gly	Ala	Leu	Pro	Gly	Met	Val	Trp	Gln	595	600	605	
Asp	Arg	Asp	Val	Tyr	Leu	Gln	Gly	Pro	Ile	Trp	Ala	Lys	Ile	Pro	His	610	615	620	
Thr	Asp	Gly	His	Phe	His	Pro	Ser	Pro	Leu	Met	Gly	Gly	Phe	Gly	Leu	625	630	635	640
Lys	Asn	Pro	Pro	Pro	Gln	Ile	Leu	Ile	Lys	Asn	Thr	Pro	Val	Pro	Ala	645	650	655	
Asn	Pro	Pro	Ala	Glu	Phe	Ser	Ala	Thr	Lys	Phe	Ala	Ser	Phe	Ile	Thr	660	665	670	
Gln	Tyr	Ser	Thr	Gly	Gln	Val	Ser	Val	Glu	Ile	Glu	Trp	Glu	Leu	Gln	675	680	685	
Lys	Glu	Asn	Ser	Lys	Arg	Trp	Asn	Pro	Glu	Val	Gln	Tyr	Thr	Ser	Asn	690	695	700	

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ggg gcc agc aac gac aac cac tac ttc ggc tac agc acc ccc tgg ggg      432
Gly Ala Ser Asn Asp Asn His Tyr Phe Gly Tyr Ser Thr Pro Trp Gly
130                               135                               140

tat ttt gat ttc aac aga ttc cac tgc cac ttt tca cca cgt gac tgg      480
Tyr Phe Asp Phe Asn Arg Phe His Cys His Phe Ser Pro Arg Asp Trp
145                               150                               155                               160

cag cga ctc atc aac aac aat tgg gga ttc cgg ccc aag aga ctc aac      528
Gln Arg Leu Ile Asn Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn
                               165                               170                               175

ttc aaa ctc ttc aac atc caa gtc aag gag gtc acg acg aat gat ggc      576
Phe Lys Leu Phe Asn Ile Gln Val Lys Glu Val Thr Thr Asn Asp Gly
                               180                               185                               190

gtc aca acc atc gct aat aac ctt acc agc acg gtt caa gtc ttc tcg      624
Val Thr Thr Ile Ala Asn Asn Leu Thr Ser Thr Val Gln Val Phe Ser
                               195                               200                               205

gac tcg gag tac cag ctt ccg tac gtc ctc ggc tct gcg cac cag ggc      672
Asp Ser Glu Tyr Gln Leu Pro Tyr Val Leu Gly Ser Ala His Gln Gly
210                               215                               220

tgc ctc cct ccg ttc ccg gcg gac gtg ttc atg att ccg caa tac ggc      720
Cys Leu Pro Pro Phe Pro Ala Asp Val Phe Met Ile Pro Gln Tyr Gly
225                               230                               235                               240

tac ctg acg ctc aac aat ggc agc caa gcc gtg gga cgt tca tcc ttt      768
Tyr Leu Thr Leu Asn Asn Gly Ser Gln Ala Val Gly Arg Ser Ser Phe
                               245                               250                               255

tac tgc ctg gaa tat ttc cct tct cag atg ctg aga acg ggc aac aac      816
Tyr Cys Leu Glu Tyr Phe Pro Ser Gln Met Leu Arg Thr Gly Asn Asn
                               260                               265                               270

ttt acc ttc agc tac acc ttt gag gaa gtg cct ttc cac agc agc tac      864
Phe Thr Phe Ser Tyr Thr Phe Glu Glu Val Pro Phe His Ser Ser Tyr
                               275                               280                               285

gcg cac agc cag agc ctg gac cgg ctg atg aat cct ctc atc gac caa      912
Ala His Ser Gln Ser Leu Asp Arg Leu Met Asn Pro Leu Ile Asp Gln
290                               295                               300

tac ctg tat tac ctg aac aga act caa aat cag tcc gga agt gcc caa      960
Tyr Leu Tyr Tyr Leu Asn Arg Thr Gln Asn Gln Ser Gly Ser Ala Gln
305                               310                               315                               320

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Asn Lys Asp Leu Leu Phe Ser Arg Gly Ser Pro Ala Gly Met Ser Val	
325 330 335	
cag ccc aaa aac tgg cta cct gga ccc tgt tat cgg cag cag cgc gtt	1056
Gln Pro Lys Asn Trp Leu Pro Gly Pro Cys Tyr Arg Gln Gln Arg Val	
340 345 350	
tct aaa aca aaa aca gac aac aac aac agc aat ttt acc tgg act ggt	1104
Ser Lys Thr Lys Thr Asp Asn Asn Asn Ser Asn Phe Thr Trp Thr Gly	
355 360 365	
gct tca aaa tat aac ctc aat ggg cgt gaa tcc atc atc aac cct ggc	1152
Ala Ser Lys Tyr Asn Leu Asn Gly Arg Glu Ser Ile Ile Asn Pro Gly	
370 375 380	
act gct atg gcc tca cac aaa gac gac gaa gac aag ttc ttt ccc atg	1200
Thr Ala Met Ala Ser His Lys Asp Asp Glu Asp Lys Phe Phe Pro Met	
385 390 395 400	
agc ggt gtc atg att ttt gga aaa gag agc gcc gga gct tca aac act	1248
Ser Gly Val Met Ile Phe Gly Lys Glu Ser Ala Gly Ala Ser Asn Thr	
405 410 415	
gca ttg gac aat gtc atg att aca gac gaa gag gaa att aaa gcc act	1296
Ala Leu Asp Asn Val Met Ile Thr Asp Glu Glu Glu Ile Lys Ala Thr	
420 425 430	
aac cct gtg gcc acc gaa aga ttt ggg acc gtg gca gtc aat ttc cag	1344
Asn Pro Val Ala Thr Glu Arg Phe Gly Thr Val Ala Val Asn Phe Gln	
435 440 445	
agc agc agc aca gac cct gcg acc gga gat gtg cat gct atg gga gca	1392
Ser Ser Ser Thr Asp Pro Ala Thr Gly Asp Val His Ala Met Gly Ala	
450 455 460	
tta cct ggc atg gtg tgg caa gat aga gac gtg tac ctg cag ggt ccc	1440
Leu Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly Pro	
465 470 475 480	
att tgg gcc aaa att cct cac aca gat gga cac ttt cac ccg tct cct	1488
Ile Trp Ala Lys Ile Pro His Thr Asp Gly His Phe His Pro Ser Pro	
485 490 495	
ctt atg ggc ggc ttt gga ctc aag aac ccg cct cct cag atc ctc atc	1536
Leu Met Gly Gly Phe Gly Leu Lys Asn Pro Pro Pro Gln Ile Leu Ile	
500 505 510	

aaa aac acg cct gtt cct gcg aat cct ccg gcg gag ttt tca gct aca 1584
 Lys Asn Thr Pro Val Pro Ala Asn Pro Pro Ala Glu Phe Ser Ala Thr
 515 520 525

aag ttt gct tca ttc atc acc caa tac tcc aca gga caa gtg agt gtg 1632
 Lys Phe Ala Ser Phe Ile Thr Gln Tyr Ser Thr Gly Gln Val Ser Val
 530 535 540

gaa att gaa tgg gag ctg cag aaa gaa aac agc aag cgc tgg aat ccc 1680
 Glu Ile Glu Trp Glu Leu Gln Lys Glu Asn Ser Lys Arg Trp Asn Pro
 545 550 555 560

gaa gtg cag tac aca tcc aat tat gca aaa tct gcc aac gtt gat ttt 1728
 Glu Val Gln Tyr Thr Ser Asn Tyr Ala Lys Ser Ala Asn Val Asp Phe
 565 570 575

act gtg gac aac aat gga ctt tat act gag cct cgc ccc att ggc acc 1776
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 580 585 590

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 Arg Tyr Leu Thr Arg Pro Leu
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 Arg Leu Asn Phe Gly Gln Thr Gly Asp Ser Glu Ser Val Pro Asp Pro
 35 40 45
 Gln Pro Leu Gly Glu Pro Pro Ala Thr Pro Ala Ala Val Gly Pro Thr
 50 55 60
 Thr Met Ala Ser Gly Gly Gly Ala Pro Met Ala Asp Asn Asn Glu Gly
 65 70 75 80
 Ala Asp Gly Val Gly Asn Ala Ser Gly Asn Trp His Cys Asp Ser Thr

				85					90						95
Trp	Leu	Gly	Asp	Arg	Val	Ile	Thr	Thr	Ser	Thr	Arg	Thr	Trp	Ala	Leu
			100					105					110		
Pro	Thr	Tyr	Asn	Asn	His	Leu	Tyr	Lys	Gln	Ile	Ser	Ser	Ala	Ser	Thr
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Asp Gly Val Gly Asn Ala Ser Gly Asn Trp His Cys Asp Ser Thr Trp
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ctg ggc gac aga gtc atc acc acc agc acc cgc acc tgg gcc ttg ccc 144
Leu Gly Asp Arg Val Ile Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro
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acc tac aat aac cac ctc tac aag caa atc tcc agt gct tca acg ggg 192
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gct atg gcc tca cac aaa gac gac gaa gac aag ttc ttt ccc atg agc	1008
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Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile
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Trp Ala Lys Ile Pro His Thr Asp Gly His Phe His Pro Ser Pro Leu
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Val Gln Tyr Thr Ser Asn Tyr Ala Lys Ser Ala Asn Val Asp Phe Thr
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 <213> AAV-1

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Glu His Leu Pro Gly Ile Ser Asp Ser Phe Val Ser Trp Val Ala Glu
 20 25 30
 Lys Glu Trp Glu Leu Pro Pro Asp Ser Asp Met Asp Leu Asn Leu Ile
 35 40 45
 Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu
 50 55 60
 Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val
 65 70 75 80
 Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu
 85 90 95
 Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile
 100 105 110
 Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu
 115 120 125
 Pro Asn Trp Phe Ala Val Thr Lys Thr Arg Asn Gly Ala Gly Gly Gly
 130 135 140
 Asn Lys Val Val Asp Glu Cys Tyr Ile Pro Asn Tyr Leu Leu Pro Lys
 145 150 155 160
 Thr Gln Pro Glu Leu Gln Trp Ala Trp Thr Asn Met Glu Glu Tyr Ile
 165 170 175
 Ser Ala Cys Leu Asn Leu Ala Glu Arg Lys Arg Leu Val Ala Gln His
 180 185 190
 Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Leu Asn
 195 200 205
 Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr
 210 215 220
 Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys
 225 230 235 240
 Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
 245 250 255
 Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
 260 265 270
 Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
 275 280 285
 Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu
 290 295 300
 Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala
 305 310 315 320
 Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala
 325 330 335

<400> 3

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
 1 5 10 15
 Glu Gly Ile Arg Glu Trp Trp Asp Leu Lys Pro Gly Ala Pro Lys Pro
 20 25 30
 Lys Ala Asn Gln Gln Lys Gln Asp Asp Gly Arg Gly Leu Val Leu Pro
 35 40 45
 Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro
 50 55 60
 Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
 65 70 75 80
 Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala
 85 90 95
 Asp Ala Glu Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly
 100 105 110
 Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro
 115 120 125
 Leu Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg
 130 135 140
 Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Ile Gly
 145 150 155 160
 Lys Thr Gly Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
 165 170 175
 Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro
 180 185 190
 Ala Thr Pro Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly
 195 200 205
 Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ala
 210 215 220
 Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val Ile
 225 230 235 240
 Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
 245 250 255
 Tyr Lys Gln Ile Ser Ser Ala Ser Thr Gly Ala Ser Asn Asp Asn His
 260 265 270
 Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe
 275 280 285
 His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Asn
 290 295 300
 Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln

305		310		315		320
Val Lys Glu Val Thr Thr Asn Asp Gly Val Thr Thr Ile Ala Asn Asn						
		325		330		335
Leu Thr Ser Thr Val Gln Val Phe Ser Asp Ser Glu Tyr Gln Leu Pro						
		340		345		350
Tyr Val Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala						
		355		360		365
Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly						
		370		375		380
Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe Pro						
		385		390		400
Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Thr Phe Ser Tyr Thr Phe						
		405		410		415
Glu Glu Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp						
		420		425		430
Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Asn Arg						
		435		440		445
Thr Gln Asn Gln Ser Gly Ser Ala Gln Asn Lys Asp Leu Leu Phe Ser						
		450		455		460
Arg Gly Ser Pro Ala Gly Met Ser Val Gln Pro Lys Asn Trp Leu Pro						
		465		470		480
Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Lys Thr Lys Thr Asp Asn						
		485		490		495
Asn Asn Ser Asn Phe Thr Trp Thr Gly Ala Ser Lys Tyr Asn Leu Asn						
		500		505		510
Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His Lys						
		515		520		525
Asp Asp Glu Asp Lys Phe Phe Pro Met Ser Gly Val Met Ile Phe Gly						
		530		535		540
Lys Glu Ser Ala Gly Ala Ser Asn Thr Ala Leu Asp Asn Val Met Ile						
		545		550		555
Thr Asp Glu Glu Glu Ile Lys Ala Thr Asn Pro Val Ala Thr Glu Arg						
		565		570		575
Phe Gly Thr Val Ala Val Asn Phe Gln Ser Ser Ser Thr Asp Pro Ala						
		580		585		590
Thr Gly Asp Val His Ala Met Gly Ala Leu Pro Gly Met Val Trp Gln						
		595		600		605
Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His						
		610		615		620
Thr Asp Gly His Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu						

625		630		635		640
Lys Asn Pro Pro	Pro Gln Ile Leu Ile	Lys Asn Thr Pro Val	Pro Ala			
	645	650	655			
Asn Pro Pro Ala	Glu Phe Ser Ala Thr	Lys Phe Ala Ser	Phe Ile Thr			
	660	665	670			
Gln Tyr Ser Thr	Gly Gln Val Ser Val	Glu Ile Glu Trp	Glu Leu Gln			
	675	680	685			
Lys Glu Asn Ser	Lys Arg Trp Asn Pro	Glu Val Gln Tyr	Thr Ser Asn			
	690	695	700			
Tyr Ala Lys Ser	Ala Asn Val Asp Phe Thr	Val Asp Asn Asn	Gly Leu			
	705	710	715			720
Tyr Thr Glu Pro	Arg Pro Ile Gly Thr	Arg Tyr Leu Thr	Arg Pro Leu			
	725	730	735			

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 <211> 1872
 <212> DNA
 <213> AAV-1

<220>
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 <222> (1)..(1869)
 <223>

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Met Pro Gly Phe Tyr Glu Ile Val Ile Lys Val Pro Ser Asp Leu Asp	
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gag cac ctg ccg ggc att tct gac tgc ttt gtg agc tgg gtg gcc gag	96
Glu His Leu Pro Gly Ile Ser Asp Ser Phe Val Ser Trp Val Ala Glu	
20 25 30	
aag gaa tgg gag ctg ccc ccg gat tct gac atg gat ctg aat ctg att	144
Lys Glu Trp Glu Leu Pro Pro Asp Ser Asp Met Asp Leu Asn Leu Ile	
35 40 45	
gag cag gca ccc ctg acc gtg gcc gag aag ctg cag cgc gac ttc ctg	192
Glu Gln Ala Pro Leu Thr Val Ala Glu Lys Leu Gln Arg Asp Phe Leu	
50 55 60	
gtc caa tgg cgc cgc gtg agt aag gcc ccg gag gcc ctc ttc ttt gtt	240
Val Gln Trp Arg Arg Val Ser Lys Ala Pro Glu Ala Leu Phe Phe Val	
65 70 75 80	
cag ttc gag aag ggc gag tcc tac ttc cac ctc cat att ctg gtg gag	288
Gln Phe Glu Lys Gly Glu Ser Tyr Phe His Leu His Ile Leu Val Glu	
85 90 95	
acc acg ggg gtc aaa tcc atg gtg ctg ggc cgc ttc ctg agt cag att	336
Thr Thr Gly Val Lys Ser Met Val Leu Gly Arg Phe Leu Ser Gln Ile	
100 105 110	

agg gac aag ctg gtg cag acc atc tac cgc ggg atc gag ccg acc ctg Arg Asp Lys Leu Val Gln Thr Ile Tyr Arg Gly Ile Glu Pro Thr Leu 115 120 125	384
ccc aac tgg ttc gcg gtg acc aag acg cgt aat ggc gcc gga ggg ggg Pro Asn Trp Phe Ala Val Thr Lys Thr Arg Asn Gly Ala Gly Gly Gly 130 135 140	432
aac aag gtg gtg gac gag tgc tac atc ccc aac tac ctc ctg ccc aag Asn Lys Val Val Asp Glu Cys Tyr Ile Pro Asn Tyr Leu Leu Pro Lys 145 150 155 160	480
act cag ccc gag ctg cag tgg gcg tgg act aac atg gag gag tat ata Thr Gln Pro Glu Leu Gln Trp Ala Trp Thr Asn Met Glu Glu Tyr Ile 165 170 175	528
agc gcc tgt ttg aac ctg gcc gag cgc aaa cgg ctc gtg gcg cag cac Ser Ala Cys Leu Asn Leu Ala Glu Arg Lys Arg Leu Val Ala Gln His 180 185 190	576
ctg acc cac gtc agc cag acc cag gag cag aac aag gag aat ctg aac Leu Thr His Val Ser Gln Thr Gln Glu Gln Asn Lys Glu Asn Leu Asn 195 200 205	624
ccc aat tct gac gcg cct gtc atc cgg tca aaa acc tcc gcg cgc tac Pro Asn Ser Asp Ala Pro Val Ile Arg Ser Lys Thr Ser Ala Arg Tyr 210 215 220	672
atg gag ctg gtc ggg tgg ctg gtg gac cgg ggc atc acc tcc gag aag Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys 225 230 235 240	720
cag tgg atc cag gag gac cag gcc tcg tac atc tcc ttc aac gcc gct Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala 245 250 255	768
tcc aac tcg cgg tcc cag atc aag gcc gct ctg gac aat gcc ggc aag Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys 260 265 270	816
atc atg gcg ctg acc aaa tcc gcg ccc gac tac ctg gta ggc ccc gct Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala 275 280 285	864
ccg ccc gcg gac att aaa acc aac cgc atc tac cgc atc ctg gag ctg Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu 290 295 300	912
aac ggc tac gaa cct gcc tac gcc ggc tcc gtc ttt ctc ggc tgg gcc Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala 305 310 315 320	960
cag aaa agg ttc ggg aag cgc aac acc atc tgg ctg ttt ggg ccg gcc Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala 325 330 335	1008
acc acg ggc aag acc aac atc gcg gaa gcc atc gcc cac gcc gtg ccc Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro 340 345 350	1056

ttc tac ggc tgc gtc aac tgg acc aat gag aac ttt ccc ttc aat gat Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp 355 360 365	1104
tgc gtc gac aag atg gtg atc tgg tgg gag gag ggc aag atg acg gcc Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala 370 375 380	1152
aag gtc gtg gag tcc gcc aag gcc att ctc ggc ggc agc aag gtg cgc Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg 385 390 395 400	1200
gtg gac caa aag tgc aag tgc tcc gcc cag atc gac ccc acc ccc gtg Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val 405 410 415	1248
atc gtc acc tcc aac acc aac atg tgc gcc gtg att gac ggg aac agc Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser 420 425 430	1296
acc acc ttc gag cac cag cag ccg ttg cag gac cgg atg ttc aaa ttt Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe 435 440 445	1344
gaa ctc acc cgc cgt ctg gag cat gac ttt ggc aag gtg aca aag cag Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln 450 455 460	1392
gaa gtc aaa gag ttc ttc cgc tgg gcg cag gat cac gtg acc gag gtg Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val 465 470 475 480	1440
gcg cat gag ttc tac gtc aga aag ggt gga gcc aac aaa aga ccc gcc Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala 485 490 495	1488
ccc gat gac gcg gat aaa agc gag ccc aag cgg gcc tgc ccc tca gtc Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val 500 505 510	1536
gcg gat cca tgc acg tca gac gcg gaa gga gct ccg gtg gac ttt gcc Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala 515 520 525	1584
gac agg tac caa aac aaa tgt tct cgt cac gcg ggc atg ctt cag atg Asp Arg Tyr Gln Asn Lys Cys Ser Arg His Ala Gly Met Leu Gln Met 530 535 540	1632
ctg ttt ccc tgc aag aca tgc gag aga atg aat cag aat ttc aac att Leu Phe Pro Cys Lys Thr Cys Glu Arg Met Asn Gln Asn Phe Asn Ile 545 550 555 560	1680
tgc ttc acg cac ggg acg aga gac tgt tca gag tgc ttc ccc ggc gtg Cys Phe Thr His Gly Thr Arg Asp Cys Ser Glu Cys Phe Pro Gly Val 565 570 575	1728
tca gaa tct caa ccg gtc gtc aga aag agg acg tat cgg aaa ctc tgt Ser Glu Ser Gln Pro Val Val Arg Lys Arg Thr Tyr Arg Lys Leu Cys 580 585 590	1776

Gln	Trp	Ile	Gln	Glu	Asp	Gln	Ala	Ser	Tyr	Ile	Ser	Phe	Asn	Ala	Ala	
				245					250					255		
Ser	Asn	Ser	Arg	Ser	Gln	Ile	Lys	Ala	Ala	Leu	Asp	Asn	Ala	Gly	Lys	
			260					265					270			
Ile	Met	Ala	Leu	Thr	Lys	Ser	Ala	Pro	Asp	Tyr	Leu	Val	Gly	Pro	Ala	
		275					280					285				
Pro	Pro	Ala	Asp	Ile	Lys	Thr	Asn	Arg	Ile	Tyr	Arg	Ile	Leu	Glu	Leu	
	290					295					300					
Asn	Gly	Tyr	Glu	Pro	Ala	Tyr	Ala	Gly	Ser	Val	Phe	Leu	Gly	Trp	Ala	
305					310					315					320	
Gln	Lys	Arg	Phe	Gly	Lys	Arg	Asn	Thr	Ile	Trp	Leu	Phe	Gly	Pro	Ala	
				325					330					335		
Thr	Thr	Gly	Lys	Thr	Asn	Ile	Ala	Glu	Ala	Ile	Ala	His	Ala	Val	Pro	
			340					345					350			
Phe	Tyr	Gly	Cys	Val	Asn	Trp	Thr	Asn	Glu	Asn	Phe	Pro	Phe	Asn	Asp	
		355					360					365				
Cys	Val	Asp	Lys	Met	Val	Ile	Trp	Trp	Glu	Glu	Gly	Lys	Met	Thr	Ala	
	370					375					380					
Lys	Val	Val	Glu	Ser	Ala	Lys	Ala	Ile	Leu	Gly	Gly	Ser	Lys	Val	Arg	
385					390					395					400	
Val	Asp	Gln	Lys	Cys	Lys	Ser	Ser	Ala	Gln	Ile	Asp	Pro	Thr	Pro	Val	
				405					410					415		
Ile	Val	Thr	Ser	Asn	Thr	Asn	Met	Cys	Ala	Val	Ile	Asp	Gly	Asn	Ser	
			420					425					430			
Thr	Thr	Phe	Glu	His	Gln	Gln	Pro	Leu	Gln	Asp	Arg	Met	Phe	Lys	Phe	
		435					440					445				
Glu	Leu	Thr	Arg	Arg	Leu	Glu	His	Asp	Phe	Gly	Lys	Val	Thr	Lys	Gln	
	450					455					460					
Glu	Val	Lys	Glu	Phe	Phe	Arg	Trp	Ala	Gln	Asp	His	Val	Thr	Glu	Val	
465					470					475				480		
Ala	His	Glu	Phe	Tyr	Val	Arg	Lys	Gly	Gly	Ala	Asn	Lys	Arg	Pro	Ala	
				485					490					495		
Pro	Asp	Asp	Ala	Asp	Lys	Ser	Glu	Pro	Lys	Arg	Ala	Cys	Pro	Ser	Val	
			500					505					510			
Ala	Asp	Pro	Ser	Thr	Ser	Asp	Ala	Glu	Gly	Ala	Pro	Val	Asp	Phe	Ala	
		515					520					525				
Asp	Arg	Tyr	Gln	Asn	Lys	Cys	Ser	Arg	His	Ala	Gly	Met	Leu	Gln	Met	
	530					535					540					
Leu	Phe	Pro	Cys	Lys	Thr	Cys	Glu	Arg	Met	Asn	Gln	Asn	Phe	Asn	Ile	
545					550					555					560	

Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala
 370 375 380
 Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg
 385 390 395 400
 Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val
 405 410 415
 Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser
 420 425 430
 Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe
 435 440 445
 Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln
 450 455 460
 Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val
 465 470 475 480
 Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala
 485 490 495
 Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val
 500 505 510
 Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
 515 520 525
 Asp Arg Tyr Gly Cys Arg Trp Leu Ser Ser Arg Leu Ala Arg Gly Gln
 530 535 540
 Pro Leu
 545

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 <212> DNA
 <213> AAV-1

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 <222> (1)..(1197)
 <223>

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 Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys
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 cag tgg atc cag gag gac cag gcc tcg tac atc tcc ttc aac gcc gct 96
 Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
 20 25 30
 tcc aac tcg cgg tcc cag atc aag gcc gct ctg gac aat gcc ggc aag 144
 Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
 35 40 45

atc atg gcg ctg acc aaa tcc gcg ccc gac tac ctg gta ggc ccc gct Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala 50 55 60	192
ccg ccc gcg gac att aaa acc aac cgc atc tac cgc atc ctg gag ctg Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu 65 70 75 80	240
aac ggc tac gaa cct gcc tac gcc ggc tcc gtc ttt ctc ggc tgg gcc Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala 85 90 95	288
cag aaa agg ttc ggg aag cgc aac acc atc tgg ctg ttt ggg ccg gcc Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala 100 105 110	336
acc acg ggc aag acc aac atc gcg gaa gcc atc gcc cac gcc gtg ccc Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro 115 120 125	384
ttc tac ggc tgc gtc aac tgg acc aat gag aac ttt ccc ttc aat gat Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp 130 135 140	432
tgc gtc gac aag atg gtg atc tgg tgg gag gag ggc aag atg acg gcc Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala 145 150 155 160	480
aag gtc gtg gag tcc gcc aag gcc att ctc ggc ggc agc aag gtg cgc Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg 165 170 175	528
gtg gac caa aag tgc aag tcg tcc gcc cag atc gac ccc acc ccc gtg Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val 180 185 190	576
atc gtc acc tcc aac acc aac atg tgc gcc gtg att gac ggg aac agc Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser 195 200 205	624
acc acc ttc gag cac cag cag ccg ttg cag gac cgg atg ttc aaa ttt Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe 210 215 220	672
gaa ctc acc cgc cgt ctg gag cat gac ttt ggc aag gtg aca aag cag Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln 225 230 235 240	720
gaa gtc aaa gag ttc ttc cgc tgg gcg cag gat cac gtg acc gag gtg Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val 245 250 255	768
gcg cat gag ttc tac gtc aga aag ggt gga gcc aac aaa aga ccc gcc Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala 260 265 270	816
ccc gat gac gcg gat aaa agc gag ccc aag cgg gcc tgc ccc tca gtc Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val 275 280 285	864

gcg gat cca tcg acg tca gac gcg gaa gga gct ccg gtg gac ttt gcc 912
 Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
 290 295 300

gac agg tac caa aac aaa tgt tct cgt cac gcg ggc atg ctt cag atg 960
 Asp Arg Tyr Gln Asn Lys Cys Ser Arg His Ala Gly Met Leu Gln Met
 305 310 315 320

ctg ttt ccc tgc aag aca tgc gag aga atg aat cag aat ttc aac att 1008
 Leu Phe Pro Cys Lys Thr Cys Glu Arg Met Asn Gln Asn Phe Asn Ile
 325 330 335

tgc ttc acg cac ggg acg aga gac tgt tca gag tgc ttc ccc ggc gtg 1056
 Cys Phe Thr His Gly Thr Arg Asp Cys Ser Glu Cys Phe Pro Gly Val
 340 345 350

tca gaa tct caa ccg gtc gtc aga aag agg acg tat cgg aaa ctc tgt 1104
 Ser Glu Ser Gln Pro Val Val Arg Lys Arg Thr Tyr Arg Lys Leu Cys
 355 360 365

gcc att cat cat ctg ctg ggg cgg gct ccc gag att gct tgc tcg gcc 1152
 Ala Ile His His Leu Leu Gly Arg Ala Pro Glu Ile Ala Cys Ser Ala
 370 375 380

tgc gat ctg gtc aac gtg gac ctg gat gac tgt gtt tct gag caa taa 1200
 Cys Asp Leu Val Asn Val Asp Leu Asp Asp Cys Val Ser Glu Gln
 385 390 395

<210> 9
 <211> 399
 <212> PRT
 <213> AAV-1

<400> 9
 Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys
 1 5 10 15

Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
 20 25 30

Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
 35 40 45

Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
 50 55 60

Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu
 65 70 75 80

Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala
 85 90 95

Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala
 100 105 110

Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro
 115 120 125

Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp

130	135	140
Cys Val Asp Lys Met	Val Ile Trp Trp Glu	Glu Gly Lys Met Thr Ala
145	150	155 160
Lys Val Val Glu Ser	Ala Lys Ala Ile Leu	Gly Gly Ser Lys Val Arg
	165	170 175
Val Asp Gln Lys Cys	Lys Ser Ser Ala Gln	Ile Asp Pro Thr Pro Val
	180	185 190
Ile Val Thr Ser Asn	Thr Asn Met Cys Ala	Val Ile Asp Gly Asn Ser
	195	200 205
Thr Thr Phe Glu His	Gln Gln Pro Leu Gln	Asp Arg Met Phe Lys Phe
	210	215 220
Glu Leu Thr Arg Arg	Leu Glu His Asp Phe	Gly Lys Val Thr Lys Gln
	225	230 235 240
Glu Val Lys Glu Phe	Phe Arg Trp Ala Gln	Asp His Val Thr Glu Val
	245	250 255
Ala His Glu Phe Tyr	Val Arg Lys Gly Gly	Ala Asn Lys Arg Pro Ala
	260	265 270
Pro Asp Asp Ala Asp	Lys Ser Glu Pro Lys	Arg Ala Cys Pro Ser Val
	275	280 285
Ala Asp Pro Ser Thr	Ser Asp Ala Glu Gly	Ala Pro Val Asp Phe Ala
	290	295 300
Asp Arg Tyr Gln Asn	Lys Cys Ser Arg His	Ala Gly Met Leu Gln Met
	305	310 315 320
Leu Phe Pro Cys Lys	Thr Cys Glu Arg Met	Asn Gln Asn Phe Asn Ile
	325	330 335
Cys Phe Thr His Gly	Thr Arg Asp Cys Ser	Glu Cys Phe Pro Gly Val
	340	345 350
Ser Glu Ser Gln Pro	Val Val Arg Lys Arg	Thr Tyr Arg Lys Leu Cys
	355	360 365
Ala Ile His His Leu	Leu Gly Arg Ala Pro	Glu Ile Ala Cys Ser Ala
	370	375 380
Cys Asp Leu Val Asn	Val Asp Leu Asp Asp	Cys Val Ser Glu Gln
	385	390 395

<210> 10
 <211> 969
 <212> DNA
 <213> AAV-1

<220>
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 <222> (1)..(966)
 <223>

<220>
 <221> misc_feature
 <222> (943)..(944)
 <223> minor splice site

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 Met Glu Leu Val Gly Trp Leu Val Asp Arg Gly Ile Thr Ser Glu Lys
 1 5 10 15
 cag tgg atc cag gag gac cag gcc tcg tac atc tcc ttc aac gcc gct 96
 Gln Trp Ile Gln Glu Asp Gln Ala Ser Tyr Ile Ser Phe Asn Ala Ala
 20 25 30
 tcc aac tcg cgg tcc cag atc aag gcc gct ctg gac aat gcc ggc aag 144
 Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
 35 40 45
 atc atg gcg ctg acc aaa tcc gcg ccc gac tac ctg gta ggc ccc gct 192
 Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
 50 55 60
 ccg ccc gcg gac att aaa acc aac cgc atc tac cgc atc ctg gag ctg 240
 Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu
 65 70 75 80
 aac ggc tac gaa cct gcc tac gcc ggc tcc gtc ttt ctc ggc tgg gcc 288
 Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala
 85 90 95
 cag aaa agg ttc ggg aag cgc aac acc atc tgg ctg ttt ggg ccg gcc 336
 Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala
 100 105 110
 acc acg ggc aag acc aac atc gcg gaa gcc atc gcc cac gcc gtg ccc 384
 Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro
 115 120 125
 ttc tac ggc tgc gtc aac tgg acc aat gag aac ttt ccc ttc aat gat 432
 Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp
 130 135 140
 tgc gtc gac aag atg gtg atc tgg tgg gag gag ggc aag atg acg gcc 480
 Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala
 145 150 155 160
 aag gtc gtg gag tcc gcc aag gcc att ctc ggc ggc agc aag gtg cgc 528
 Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg
 165 170 175
 gtg gac caa aag tgc aag tcg tcc gcc cag atc gac ccc acc ccc gtg 576
 Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val
 180 185 190
 atc gtc acc tcc aac acc aac atg tgc gcc gtg att gac ggg aac agc 624
 Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser
 195 200 205
 acc acc ttc gag cac cag cag ccg ttg cag gac cgg atg ttc aaa ttt 672

Thr	Thr	Phe	Glu	His	Gln	Gln	Pro	Leu	Gln	Asp	Arg	Met	Phe	Lys	Phe		
	210					215					220						
720																	
gaa	ctc	acc	cgc	cgt	ctg	gag	cat	gac	ttt	ggc	aag	gtg	aca	aag	cag		
Glu	Leu	Thr	Arg	Arg	Leu	Glu	His	Asp	Phe	Gly	Lys	Val	Thr	Lys	Gln		
225					230				235						240		
768																	
gaa	gtc	aaa	gag	ttc	ttc	cgc	tgg	gcg	cag	gat	cac	gtg	acc	gag	gtg		
Glu	Val	Lys	Glu	Phe	Phe	Arg	Trp	Ala	Gln	Asp	His	Val	Thr	Glu	Val		
				245					250					255			
816																	
gcg	cat	gag	ttc	tac	gtc	aga	aag	ggg	gga	gcc	aac	aaa	aga	ccc	gcc		
Ala	His	Glu	Phe	Tyr	Val	Arg	Lys	Gly	Gly	Ala	Asn	Lys	Arg	Pro	Ala		
			260					265					270				
864																	
ccc	gat	gac	gcg	gat	aaa	agc	gag	ccc	aag	cgg	gcc	tgc	ccc	tca	gtc		
Pro	Asp	Asp	Ala	Asp	Lys	Ser	Glu	Pro	Lys	Arg	Ala	Cys	Pro	Ser	Val		
		275					280					285					
912																	
gcg	gat	cca	tcg	acg	tca	gac	gcg	gaa	gga	gct	ccg	gtg	gac	ttt	gcc		
Ala	Asp	Pro	Ser	Thr	Ser	Asp	Ala	Glu	Gly	Ala	Pro	Val	Asp	Phe	Ala		
	290					295					300						
960																	
gac	agg	tat	ggc	tgc	cga	tgg	tta	tct	tcc	aga	ttg	gct	cga	gga	caa		
Asp	Arg	Tyr	Gly	Cys	Arg	Trp	Leu	Ser	Ser	Arg	Leu	Ala	Arg	Gly	Gln		
305					310					315					320		
969																	
cct	ctc	tga															
Pro	Leu																

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 <213> AAV-1

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 <223> minor splice site

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 Ser Asn Ser Arg Ser Gln Ile Lys Ala Ala Leu Asp Asn Ala Gly Lys
 35 40 45
 Ile Met Ala Leu Thr Lys Ser Ala Pro Asp Tyr Leu Val Gly Pro Ala
 50 55 60
 Pro Pro Ala Asp Ile Lys Thr Asn Arg Ile Tyr Arg Ile Leu Glu Leu
 65 70 75 80
 Asn Gly Tyr Glu Pro Ala Tyr Ala Gly Ser Val Phe Leu Gly Trp Ala
 85 90 95

Gln Lys Arg Phe Gly Lys Arg Asn Thr Ile Trp Leu Phe Gly Pro Ala
 100 105 110
 Thr Thr Gly Lys Thr Asn Ile Ala Glu Ala Ile Ala His Ala Val Pro
 115 120 125
 Phe Tyr Gly Cys Val Asn Trp Thr Asn Glu Asn Phe Pro Phe Asn Asp
 130 135 140
 Cys Val Asp Lys Met Val Ile Trp Trp Glu Glu Gly Lys Met Thr Ala
 145 150 155 160
 Lys Val Val Glu Ser Ala Lys Ala Ile Leu Gly Gly Ser Lys Val Arg
 165 170 175
 Val Asp Gln Lys Cys Lys Ser Ser Ala Gln Ile Asp Pro Thr Pro Val
 180 185 190
 Ile Val Thr Ser Asn Thr Asn Met Cys Ala Val Ile Asp Gly Asn Ser
 195 200 205
 Thr Thr Phe Glu His Gln Gln Pro Leu Gln Asp Arg Met Phe Lys Phe
 210 215 220
 Glu Leu Thr Arg Arg Leu Glu His Asp Phe Gly Lys Val Thr Lys Gln
 225 230 235 240
 Glu Val Lys Glu Phe Phe Arg Trp Ala Gln Asp His Val Thr Glu Val
 245 250 255
 Ala His Glu Phe Tyr Val Arg Lys Gly Gly Ala Asn Lys Arg Pro Ala
 260 265 270
 Pro Asp Asp Ala Asp Lys Ser Glu Pro Lys Arg Ala Cys Pro Ser Val
 275 280 285
 Ala Asp Pro Ser Thr Ser Asp Ala Glu Gly Ala Pro Val Asp Phe Ala
 290 295 300
 Asp Arg Tyr Gly Cys Arg Trp Leu Ser Ser Arg Leu Ala Arg Gly Gln
 305 310 315 320
 Pro Leu

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 <212> DNA
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<220>
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 Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser

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gag ggc att cgc gag tgg tgg gac ttg aaa cct gga gcc ccg aag ccc Glu Gly Ile Arg Glu Trp Trp Asp Leu Lys Pro Gly Ala Pro Lys Pro	20	25	30	96
aaa gcc aac cag caa aag cag gac gac ggc cgg ggt ctg gtg ctt cct Lys Ala Asn Gln Gln Lys Gln Asp Asp Gly Arg Gly Leu Val Leu Pro	35	40	45	144
ggc tac aag tac ctc gga ccc ttc aac gga ctc gac aag ggg gag ccc Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro	50	55	60	192
gtc aac gcg gcg gac gca gcg gcc ctc gag cac gac aag gcc tac gac Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp	65	70	75	240
cag cag ctc aaa gcg ggt gac aat ccg tac ctg cgg tat aac cac gcc Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala	85	90	95	288
gac gcc gag ttt cag gag cgt ctg caa gaa gat acg tct ttt ggg ggc Asp Ala Glu Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly	100	105	110	336
aac ctc ggg cga gca gtc ttc cag gcc aag aag cgg gtt ctc gaa cct Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro	115	120	125	384
ctc ggt ctg gtt gag gaa ggc gct aag acg gct cct gga aag aaa cgt Leu Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg	130	135	140	432
ccg gta gag cag tcg cca caa gag cca gac tcc tcc tcg ggc atc ggc Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Ile Gly	145	150	155	480
aag aca ggc cag cag ccc gct aaa aag aga ctc aat ttt ggt cag act Lys Thr Gly Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr	165	170	175	528
ggc gac tca gag tca gtc ccc gat cca caa cct ctc gga gaa cct cca Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro	180	185	190	576
gca acc ccc gct gct gtg gga cct act aca atg gct tca ggc ggt ggc Ala Thr Pro Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly	195	200	205	624
gca cca atg gca gac aat aac gaa ggc gcc gac gga gtg ggt aat gcc Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ala	210	215	220	672
tca gga aat tgg cat tgc gat tcc aca tgg ctg ggc gac aga gtc atc Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val Ile	225	230	235	720
acc acc agc acc cgc acc tgg gcc ttg ccc acc tac aat aac cac ctc Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu				768

				245				250				255							
tac	aag	caa	atc	tcc	agt	gct	tca	acg	ggg	gcc	agc	aac	gac	aac	cac	816			
Tyr	Lys	Gln	Ile	Ser	Ser	Ala	Ser	Thr	Gly	Ala	Ser	Asn	Asp	Asn	His				
260								265				270							
tac	ttc	ggc	tac	agc	acc	ccc	tgg	ggg	tat	ttt	gat	ttc	aac	aga	ttc	864			
Tyr	Phe	Gly	Tyr	Ser	Thr	Pro	Trp	Gly	Tyr	Phe	Asp	Phe	Asn	Arg	Phe				
275								280				285							
cac	tgc	cac	ttt	tca	cca	cgt	gac	tgg	cag	cga	ctc	atc	aac	aac	aat	912			
His	Cys	His	Phe	Ser	Pro	Arg	Asp	Trp	Gln	Arg	Leu	Ile	Asn	Asn	Asn				
290								295				300							
tgg	gga	ttc	cgg	ccc	aag	aga	ctc	aac	ttc	aaa	ctc	ttc	aac	atc	caa	960			
Trp	Gly	Phe	Arg	Pro	Lys	Arg	Leu	Asn	Phe	Lys	Leu	Phe	Asn	Ile	Gln				
305								310				315				320			
gtc	aag	gag	gtc	acg	acg	aat	gat	ggc	gtc	aca	acc	atc	gct	aat	aac	1008			
Val	Lys	Glu	Val	Thr	Thr	Asn	Asp	Gly	Val	Thr	Thr	Ile	Ala	Asn	Asn				
				325				330				335							
ctt	acc	agc	acg	gtt	caa	gtc	ttc	tcg	gac	tcg	gag	tac	cag	ctt	ccg	1056			
Leu	Thr	Ser	Thr	Val	Gln	Val	Phe	Ser	Asp	Ser	Glu	Tyr	Gln	Leu	Pro				
				340				345				350							
tac	gtc	ctc	ggc	tct	gcg	cac	cag	ggc	tgc	ctc	cct	ccg	ttc	ccg	gcg	1104			
Tyr	Val	Leu	Gly	Ser	Ala	His	Gln	Gly	Cys	Leu	Pro	Pro	Phe	Pro	Ala				
				355				360				365							
gac	gtg	ttc	atg	att	ccg	caa	tac	ggc	tac	ctg	acg	ctc	aac	aat	ggc	1152			
Asp	Val	Phe	Met	Ile	Pro	Gln	Tyr	Gly	Tyr	Leu	Thr	Leu	Asn	Asn	Gly				
				370				375				380							
agc	caa	gcc	gtg	gga	cgt	tca	tcc	ttt	tac	tgc	ctg	gaa	tat	ttc	cct	1200			
Ser	Gln	Ala	Val	Gly	Arg	Ser	Ser	Phe	Tyr	Cys	Leu	Glu	Tyr	Phe	Pro				
				385				390				395				400			
tct	cag	atg	ctg	aga	acg	ggc	aac	aac	ttt	acc	ttc	agc	tac	acc	ttt	1248			
Ser	Gln	Met	Leu	Arg	Thr	Gly	Asn	Asn	Phe	Thr	Phe	Ser	Tyr	Thr	Phe				
				405				410				415							
gag	gaa	gtg	cct	ttc	cac	agc	agc	tac	gcg	cac	agc	cag	agc	ctg	gac	1296			
Glu	Glu	Val	Pro	Phe	His	Ser	Ser	Tyr	Ala	His	Ser	Gln	Ser	Leu	Asp				
				420				425				430							
cgg	ctg	atg	aat	cct	ctc	atc	gac	caa	tac	ctg	tat	tac	ctg	aac	aga	1344			
Arg	Leu	Met	Asn	Pro	Leu	Ile	Asp	Gln	Tyr	Leu	Tyr	Tyr	Leu	Asn	Arg				
				435				440				445							
act	caa	aat	cag	tcc	gga	agt	gcc	caa	aac	aag	gac	ttg	ctg	ttt	agc	1392			
Thr	Gln	Asn	Gln	Ser	Gly	Ser	Ala	Gln	Asn	Lys	Asp	Leu	Leu	Phe	Ser				
				450				455				460							
cgt	ggg	tct	cca	gct	ggc	atg	tct	gtt	cag	ccc	aaa	aac	tgg	cta	cct	1440			
Arg	Gly	Ser	Pro	Ala	Gly	Met	Ser	Val	Gln	Pro	Lys	Asn	Trp	Leu	Pro				
				465				470				475				480			
gga	ccc	tgt	tat	cgg	cag	cag	cgc	gtt	tct	aaa	aca	aaa	aca	gac	aac	1488			
Gly	Pro	Cys	Tyr	Arg	Gln	Gln	Arg	Val	Ser	Lys	Thr	Lys	Thr	Asp	Asn				

485										490					495					
aac	aac	agc	aat	ttt	acc	tgg	act	ggt	gct	tca	aaa	tat	aac	ctc	aat	1536				
Asn	Asn	Ser	Asn	Phe	Thr	Trp	Thr	Gly	Ala	Ser	Lys	Tyr	Asn	Leu	Asn					
			500					505					510							
ggg	cgt	gaa	tcc	atc	atc	aac	cct	ggc	act	gct	atg	gcc	tca	cac	aaa	1584				
Gly	Arg	Glu	Ser	Ile	Ile	Asn	Pro	Gly	Thr	Ala	Met	Ala	Ser	His	Lys					
		515					520					525								
gac	gac	gaa	gac	aag	ttc	ttt	ccc	atg	agc	ggt	gtc	atg	att	ttt	gga	1632				
Asp	Asp	Glu	Asp	Lys	Phe	Phe	Pro	Met	Ser	Gly	Val	Met	Ile	Phe	Gly					
		530				535					540									
aaa	gag	agc	gcc	gga	gct	tca	aac	act	gca	ttg	gac	aat	gtc	atg	att	1680				
Lys	Glu	Ser	Ala	Gly	Ala	Ser	Asn	Thr	Ala	Leu	Asp	Asn	Val	Met	Ile					
545					550					555					560					
aca	gac	gaa	gag	gaa	att	aaa	gcc	act	aac	cct	gtg	gcc	acc	gaa	aga	1728				
Thr	Asp	Glu	Glu	Glu	Ile	Lys	Ala	Thr	Asn	Pro	Val	Ala	Thr	Glu	Arg					
				565						570				575						
ttt	ggg	acc	gtg	gca	gtc	aat	ttc	cag	agc	agc	agc	aca	gac	cct	gcg	1776				
Phe	Gly	Thr	Val	Ala	Val	Asn	Phe	Gln	Ser	Ser	Ser	Thr	Asp	Pro	Ala					
			580					585					590							
acc	gga	gat	gtg	cat	gct	atg	gga	gca	tta	cct	ggc	atg	gtg	tgg	caa	1824				
Thr	Gly	Asp	Val	His	Ala	Met	Gly	Ala	Leu	Pro	Gly	Met	Val	Trp	Gln					
		595				600						605								
gat	aga	gac	gtg	tac	ctg	cag	ggt	ccc	att	tgg	gcc	aaa	att	cct	cac	1872				
Asp	Arg	Asp	Val	Tyr	Leu	Gln	Gly	Pro	Ile	Trp	Ala	Lys	Ile	Pro	His					
	610					615					620									
aca	gat	gga	cac	ttt	cac	ccg	tct	cct	ctt	atg	ggc	ggc	ttt	gga	ctc	1920				
Thr	Asp	Gly	His	Phe	His	Pro	Ser	Pro	Leu	Met	Gly	Gly	Phe	Gly	Leu					
625					630					635					640					
aag	aac	ccg	cct	cct	cag	atc	ctc	atc	aaa	aac	acg	cct	gtt	cct	gcg	1968				
Lys	Asn	Pro	Pro	Pro	Gln	Ile	Leu	Ile	Lys	Asn	Thr	Pro	Val	Pro	Ala					
				645					650					655						
aat	cct	ccg	gcg	gag	ttt	tca	gct	aca	aag	ttt	gct	tca	ttc	atc	acc	2016				
Asn	Pro	Pro	Ala	Glu	Phe	Ser	Ala	Thr	Lys	Phe	Ala	Ser	Phe	Ile	Thr					
			660					665					670							
caa	tac	tcc	aca	gga	caa	gtg	agt	gtg	gaa	att	gaa	tgg	gag	ctg	cag	2064				
Gln	Tyr	Ser	Thr	Gly	Gln	Val	Ser	Val	Glu	Ile	Glu	Trp	Glu	Leu	Gln					
			675				680					685								
aaa	gaa	aac	agc	aag	cgc	tgg	aat	ccc	gaa	gtg	cag	tac	aca	tcc	aat	2112				
Lys	Glu	Asn	Ser	Lys	Arg	Trp	Asn	Pro	Glu	Val	Gln	Tyr	Thr	Ser	Asn					
	690					695					700									
tat	gca	aaa	tct	gcc	aac	gtt	gat	ttt	act	gtg	gac	aac	aat	gga	ctt	2160				
Tyr	Ala	Lys	Ser	Ala	Asn	Val	Asp	Phe	Thr	Val	Asp	Asn	Asn	Gly	Leu					
705					710					715					720					
tat	act	gag	cct	cgc	ccc	att	ggc	acc	cgt	tac	ctt	acc	cgt	ccc	ctg	2208				
Tyr	Thr	Glu	Pro	Arg	Pro	Ile	Gly	Thr	Arg	Tyr	Leu	Thr	Arg	Pro	Leu					

725

730

735

2211

taa

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 <212> PRT
 <213> AAV-1

<400> 13

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Glu Gly Ile Arg Glu Trp Trp Asp Leu Lys Pro Gly Ala Pro Lys Pro
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Lys Ala Asn Gln Gln Lys Gln Asp Asp Gly Arg Gly Leu Val Leu Pro
 35 40 45

Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro
 50 55 60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
 65 70 75 80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala
 85 90 95

Asp Ala Glu Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly
 100 105 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro
 115 120 125

Leu Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg
 130 135 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Ile Gly
 145 150 155 160

Lys Thr Gly Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
 165 170 175

Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro
 180 185 190

Ala Thr Pro Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly
 195 200 205

Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ala
 210 215 220

Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val Ile
 225 230 235 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
 245 250 255

Tyr Lys Gln Ile Ser Ser Ala Ser Thr Gly Ala Ser Asn Asp Asn His

580					585					590					
Thr	Gly	Asp	Val	His	Ala	Met	Gly	Ala	Leu	Pro	Gly	Met	Val	Trp	Gln
		595					600					605			
Asp	Arg	Asp	Val	Tyr	Leu	Gln	Gly	Pro	Ile	Trp	Ala	Lys	Ile	Pro	His
	610					615					620				
Thr	Asp	Gly	His	Phe	His	Pro	Ser	Pro	Leu	Met	Gly	Gly	Phe	Gly	Leu
	625					630					635				640
Lys	Asn	Pro	Pro	Pro	Gln	Ile	Leu	Ile	Lys	Asn	Thr	Pro	Val	Pro	Ala
				645					650					655	
Asn	Pro	Pro	Ala	Glu	Phe	Ser	Ala	Thr	Lys	Phe	Ala	Ser	Phe	Ile	Thr
			660					665					670		
Gln	Tyr	Ser	Thr	Gly	Gln	Val	Ser	Val	Glu	Ile	Glu	Trp	Glu	Leu	Gln
		675					680					685			
Lys	Glu	Asn	Ser	Lys	Arg	Trp	Asn	Pro	Glu	Val	Gln	Tyr	Thr	Ser	Asn
	690					695					700				
Tyr	Ala	Lys	Ser	Ala	Asn	Val	Asp	Phe	Thr	Val	Asp	Asn	Asn	Gly	Leu
	705					710					715				720
Tyr	Thr	Glu	Pro	Arg	Pro	Ile	Gly	Thr	Arg	Tyr	Leu	Thr	Arg	Pro	Leu
				725					730					735	

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 <212> DNA
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1				5					10					15		
gac tcc tcc tcg ggc atc ggc aag aca ggc cag cag ccc gct aaa aag															96	
Asp	Ser	Ser	Ser	Gly	Ile	Gly	Lys	Thr	Gly	Gln	Gln	Pro	Ala	Lys	Lys	
			20					25					30			
aga ctc aat ttt ggt cag act ggc gac tca gag tca gtc ccc gat cca															144	
Arg	Leu	Asn	Phe	Gly	Gln	Thr	Gly	Asp	Ser	Glu	Ser	Val	Pro	Asp	Pro	
		35					40					45				
caa cct ctc gga gaa cct cca gca acc ccc gct gct gtg gga cct act															192	
Gln	Pro	Leu	Gly	Glu	Pro	Pro	Ala	Thr	Pro	Ala	Val	Gly	Pro	Thr		
		50				55				60						
aca atg gct tca ggc ggt ggc gca cca atg gca gac aat aac gaa ggc															240	
Thr	Met	Ala	Ser	Gly	Gly	Gly	Ala	Pro	Met	Ala	Asp	Asn	Asn	Glu	Gly	
	65				70					75				80		

gcc gac gga gtg ggt aat gcc tca gga aat tgg cat tgc gat tcc aca Ala Asp Gly Val Gly Asn Ala Ser Gly Asn Trp His Cys Asp Ser Thr 85 90 95	288
tgg ctg ggc gac aga gtc atc acc acc agc acc cgc acc tgg gcc ttg Trp Leu Gly Asp Arg Val Ile Thr Thr Ser Thr Arg Thr Trp Ala Leu 100 105 110	336
ccc acc tac aat aac cac ctc tac aag caa atc tcc agt gct tca acg Pro Thr Tyr Asn Asn His Leu Tyr Lys Gln Ile Ser Ser Ala Ser Thr 115 120 125	384
ggg gcc agc aac gac aac cac tac ttc ggc tac agc acc ccc tgg ggg Gly Ala Ser Asn Asp Asn His Tyr Phe Gly Tyr Ser Thr Pro Trp Gly 130 135 140	432
tat ttt gat ttc aac aga ttc cac tgc cac ttt tca cca cgt gac tgg Tyr Phe Asp Phe Asn Arg Phe His Cys His Phe Ser Pro Arg Asp Trp 145 150 155 160	480
cag cga ctc atc aac aac aat tgg gga ttc cgg ccc aag aga ctc aac Gln Arg Leu Ile Asn Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn 165 170 175	528
ttc aaa ctc ttc aac atc caa gtc aag gag gtc acg acg aat gat ggc Phe Lys Leu Phe Asn Ile Gln Val Lys Glu Val Thr Thr Asn Asp Gly 180 185 190	576
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gac tcg gag tac cag ctt ccg tac gtc ctc ggc tct gcg cac cag ggc Asp Ser Glu Tyr Gln Leu Pro Tyr Val Leu Gly Ser Ala His Gln Gly 210 215 220	672
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act gtg gac aac aat gga ctt tat act gag cct cgc ccc att ggc acc 1776
Thr Val Asp Asn Asn Gly Leu Tyr Thr Glu Pro Arg Pro Ile Gly Thr
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 Arg Tyr Leu Thr Arg Pro Leu
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Arg	Leu	Asn 35	Phe	Gly	Gln	Thr	Gly 40	Asp	Ser	Glu	Ser	Val 45	Pro	Asp	Pro	
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Thr 65	Met	Ala	Ser	Gly	Gly 70	Gly	Ala	Pro	Met	Ala 75	Asp	Asn	Asn	Glu	Gly 80	
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Pro	Thr	Tyr 115	Asn	Asn	His	Leu	Tyr 120	Lys	Gln	Ile	Ser	Ser 125	Ala	Ser	Thr	
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Val	Thr	Thr 195	Ile	Ala	Asn	Asn	Leu 200	Thr	Ser	Thr	Val	Gln 205	Val	Phe	Ser	
Asp	Ser	Glu	Tyr	Gln	Leu	Pro	Tyr	Val	Leu	Gly	Ser	Ala	His	Gln	Gly	

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Glu Ile Glu Trp Glu Leu Gln Lys Glu Asn Ser Lys Arg Trp Asn Pro
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Glu Val Gln Tyr Thr Ser Asn Tyr Ala Lys Ser Ala Asn Val Asp Phe
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ctg ggc gac aga gtc atc acc acc agc acc cgc acc tgg gcc ttg ccc 144
 Leu Gly Asp Arg Val Ile Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro
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acc tac aat aac cac ctc tac aag caa atc tcc agt gct tca acg ggg 192
 Thr Tyr Asn Asn His Leu Tyr Lys Gln Ile Ser Ser Ala Ser Thr Gly
 50 55 60

gcc agc aac gac aac cac tac ttc ggc tac agc acc ccc tgg ggg tat 240
 Ala Ser Asn Asp Asn His Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr
 65 70 75 80

ttt gat ttc aac aga ttc cac tgc cac ttt tca cca cgt gac tgg cag 288
 Phe Asp Phe Asn Arg Phe His Cys His Phe Ser Pro Arg Asp Trp Gln
 85 90 95

cga ctc atc aac aac aat tgg gga ttc cgg ccc aag aga ctc aac ttc 336
 Arg Leu Ile Asn Asn Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe
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 Lys Leu Phe Asn Ile Gln Val Lys Glu Val Thr Thr Asn Asp Gly Val
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 Thr Thr Ile Ala Asn Asn Leu Thr Ser Thr Val Gln Val Phe Ser Asp

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ctg acg ctc aac aat ggc agc caa gcc gtg gga cgt tca tcc ttt tac Leu Thr Leu Asn Asn Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr 180 185 190			576
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Pro Gly Met Val Trp Gln Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile			
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Trp Ala Lys Ile Pro His Thr Asp Gly His Phe His Pro Ser Pro Leu			
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Phe Ala Ser Phe Ile Thr Gln Tyr Ser Thr Gly Gln Val Ser Val Glu			
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Ile Glu Trp Glu Leu Gln Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu			
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Val Gln Tyr Thr Ser Asn Tyr Ala Lys Ser Ala Asn Val Asp Phe Thr			
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Val Asp Asn Asn Gly Leu Tyr Thr Glu Pro Arg Pro Ile Gly Thr Arg			
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 35 40 45
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Lys	Leu	Phe	Asn	Ile	Gln	Val	Lys	Glu	Val	Thr	Thr	Asn	Asp	Gly	Val	
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Thr	Thr	Ile	Ala	Asn	Asn	Leu	Thr	Ser	Thr	Val	Gln	Val	Phe	Ser	Asp	
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Cys	Leu	Glu	Tyr	Phe	Pro	Ser	Gln	Met	Leu	Arg	Thr	Gly	Asn	Asn	Phe	
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Lys	Asp	Leu	Leu	Phe	Ser	Arg	Gly	Ser	Pro	Ala	Gly	Met	Ser	Val	Gln	
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 Phe Ala Ser Phe Ile Thr Gln Tyr Ser Thr Gly Gln Val Ser Val Glu
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